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THIAZOLINE RING FORMATION FROM 2-METHYLCYSTEINES AND 2-HALOMETHYLALANINES

Brant L. Kedrowski and Clayton H. Heathcock*

Department of Chemistry and Center for New Directions in Organic Synthesis,‡
University of California, Berkeley, California 94720, USA
heathcock@cchem.berkeley.edu

Abstract - A systematic survey of conditions and substrates for the formation of 2,4,4-trisubstituted thiazoline rings is presented. The substitution patterns of these thiazolines is particularly relevant for the synthesis of the tantazole, mirabazole, and thiangazole classes of natural products, which contain a linear array of these heterocycles. Methods for the formation of these thiazolines from 2-methyl cysteines and 2-halomethylalanines are discussed.

INTRODUCTION

Thiazoline rings are important reoccurring structural elements that appear in a variety of natural products. We are particularly interested in the tantazoles (**1**),[1a,b] mirabazoles (**2**),[2] and thiangazole (**3**)[3] natural products, which contain a linear array of fused thiazolines (Figure 1).

In addition to their interesting polyheterocyclic structures, these compounds have demonstrated significant biological activity. Members of the tantazole and mirabazole families have displayed selective cytotoxicity against murine solid tumors, and thiangazole has been reported to be a potent and selective inhibitor HIV-1.[3,4]

A number of total syntheses of the tantazoles,[5] mirabazoles,[6] and thiangazole[7] have been reported, including contributions from our own group. Our strategy is based on a biomimetic approach, in which the thiazoline rings derive from the cysteine residues of a peptide, and is illustrated below in the synthesis of mirabazole B (**2**, Scheme 1).[6e] In this approach, a poly-2-methylcysteine peptide (**4**) is constructed *via* standard peptide coupling chemistry, and the thiazoline rings are then simultaneously formed by a cyclodehydration reaction to give **5**.

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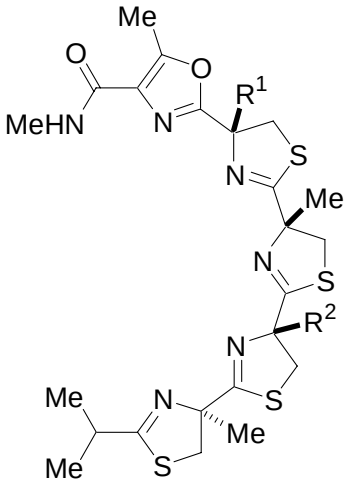
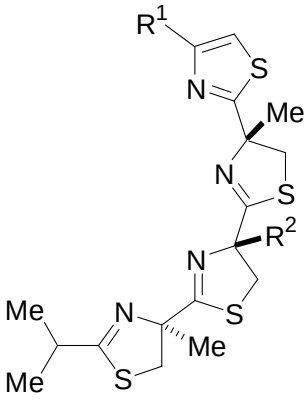
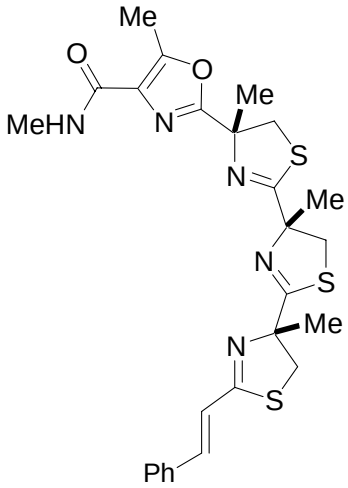
Figure 1



tantazoles A, B, F, I (**1**)
A: R^1=H; R^2=Me
B: R^1=Me; R^2=Me
F: R^1=Me; R^2=αH
I: R^1=Me; R^2=βH

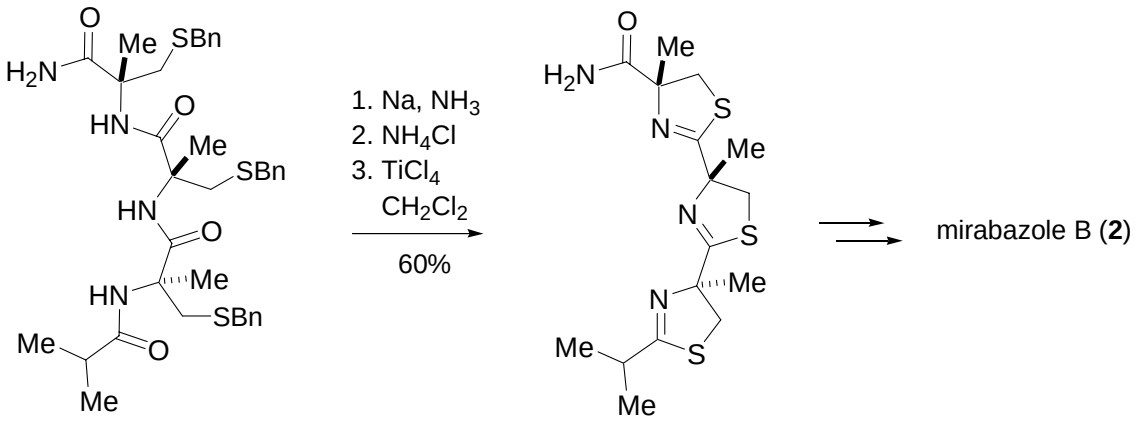


mirabazoles A, B, C (**2**)
A: R^1=Me; R^2=H
B: R^1=Me; R^2=Me
C: R^1=H; R^2=Me



thiangazole (**3**)

Scheme 1



4 **5**

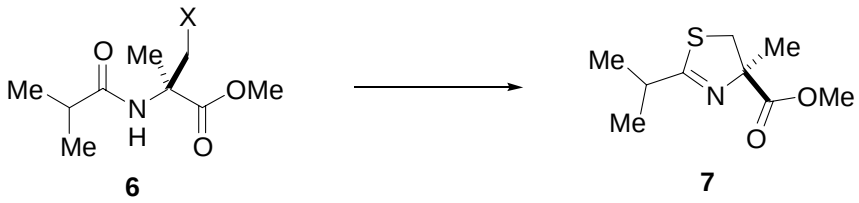
Our interest in these polythiazoline compounds has prompted us to explore more efficient and/or faster methods toward their synthesis. Since these molecules are derived from peptides, they seem particularly well suited for solid-phase synthesis. The development of a solid-phase approach to these polythiazoline compounds should greatly facilitate their synthesis. This would in turn allow for rapid production of analogs, which will be useful in the further exploration of their promising biological activities. Ideally, we wanted a solid-phase synthesis in which nearly all synthetic operations, including amino acid coupling and thiazoline formation, could be done on resin, and the finished product cleaved with little or no

subsequent modification required. Of primary concern in this approach was the ability to form thiazoline rings on a solid support. The conditions used to carry out this transformation in solution phase involved a dissolving metal debenzylation and were predicted to be incompatible with a polystyrene-based support. To circumvent this problem, a number of alternative methods for thiazoline formation were explored. Additionally, we were interested in finding methods that could accomplish thiazoline cyclization in a single step, and not require a separate sulfur deprotection step as in Scheme 1. This paper deals with the exploration of these methods in solution-phase in model systems.

RESULTS AND DISCUSSION

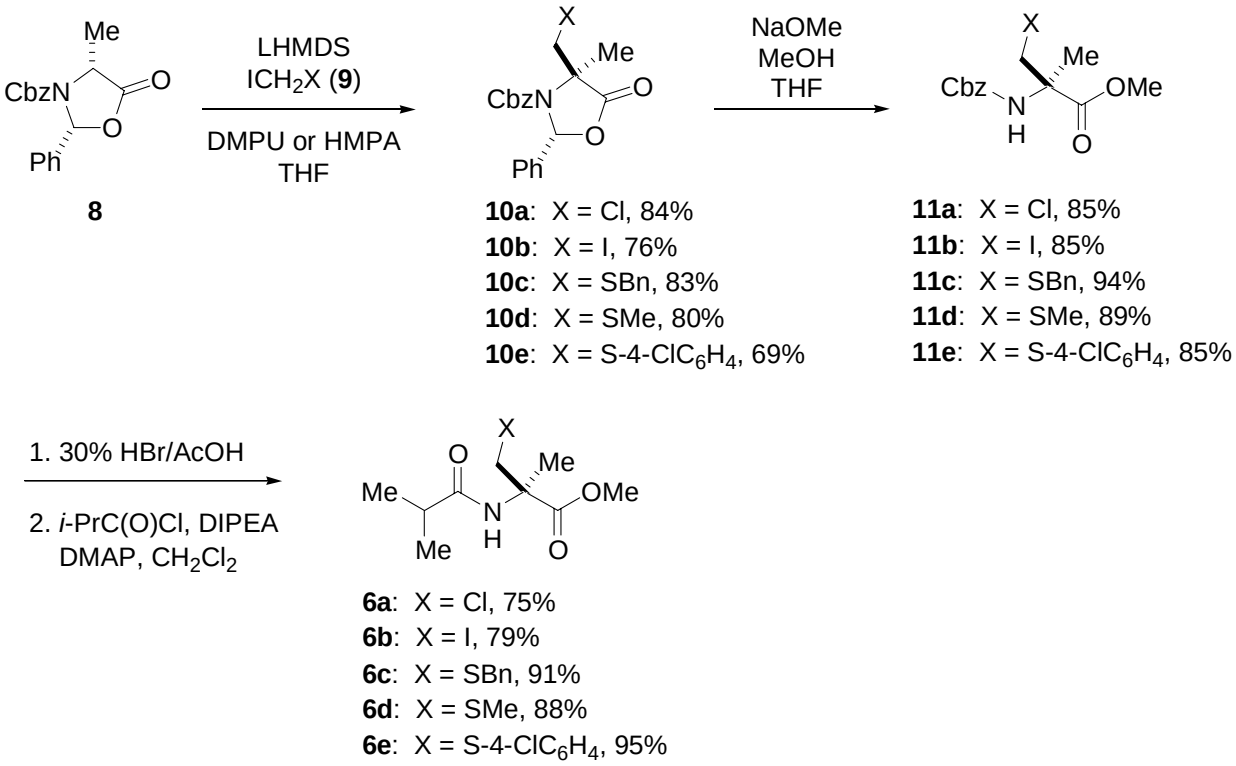
A Simple Model For Thiazoline Formation. Conversion of the simple model substrate (**6**) to **7**[a,c] (Scheme 2) was chosen as a starting point for the evaluation of thiazoline forming conditions. Both 2-methylcysteine and 2-halomethylalanine based substrates, where X = S-R and halide respectively, were examined.

Scheme 2



The synthesis of **6** is described in Scheme 3. From alanine, the oxazolidone (**8**) was prepared in optically pure form as reported previously.[8,7a] Deprotonation of **8** with LHMDS at low temperatures, followed by treatment with **9** gave the alkylation product (**10**) in good yield with complete facial selectivity. Treatment of **10** with sodium methoxide in methanol resulted in oxazolidone fragmentation and formation of the methyl ester (**11**). Finally, in a two step procedure, the benzyloxycarbonyl protecting group of **11** was removed with HBr in acetic acid, and the free nitrogen acylated with isobutyryl chloride to give **6**. This acylation proceeded smoothly in each example with the exception of the iodo substrate (**6b**). Under the reaction conditions used for the other substrates, **6b** forms but then undergoes cyclization with elimination of iodide to give the oxazoline (**12**) (Scheme 4). This cyclization is promoted by base, but is slow enough at −78 °C that the outcome can be controlled. Quenching with acid at low temperatures gave the amide (**6b**), and allowing this substrate to warm in the presence of base led to **12**. The amide (**6b**) could be converted to **12** by heating with DBU.

Scheme 3



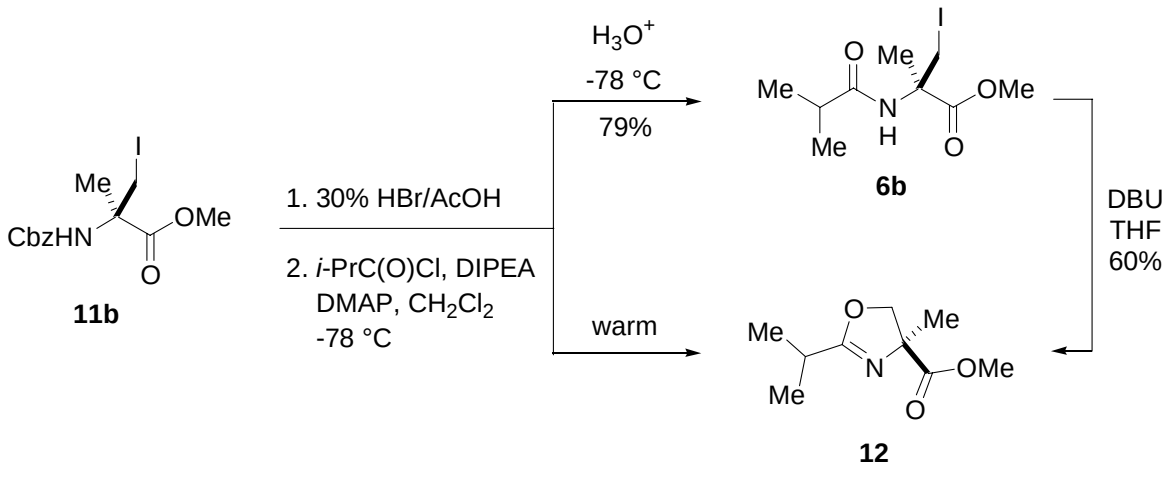
8

10a: X = Cl, 84%
10b: X = I, 76%
10c: X = SBn, 83%
10d: X = SMe, 80%
10e: X = S-4-ClC_6H_4, 69%

11a: X = Cl, 85%
11b: X = I, 85%
11c: X = SBn, 94%
11d: X = SMe, 89%
11e: X = S-4-ClC_6H_4, 85%

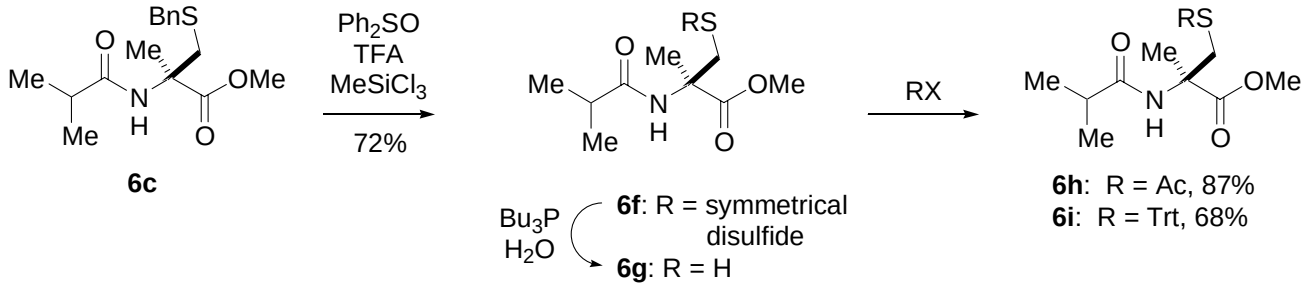
6a: X = Cl, 75%
6b: X = I, 79%
6c: X = SBn, 91%
6d: X = SMe, 88%
6e: X = S-4-ClC_6H_4, 95%

Scheme 4



In addition to **6a-e**, we were also interested in obtaining substrates which were not readily available from the route in Scheme 3 due to the inaccessibility of the alkylating agent (**9**). For the preparation of these molecules, an alternate strategy is described in Scheme 5. In this route, the benzyl thioether of **6c** is cleaved with diphenyl sulfoxide and methyltrichlorosilane in TFA[9] to give the symmetrical disulfide (**6f**). Reduction of the disulfide bond with tributylphosphine gave the mercaptan (**6g**), which was followed by treatment with acetic anhydride or trityl alcohol in TFA to give **6h** and **6i**, respectively.

Scheme 5



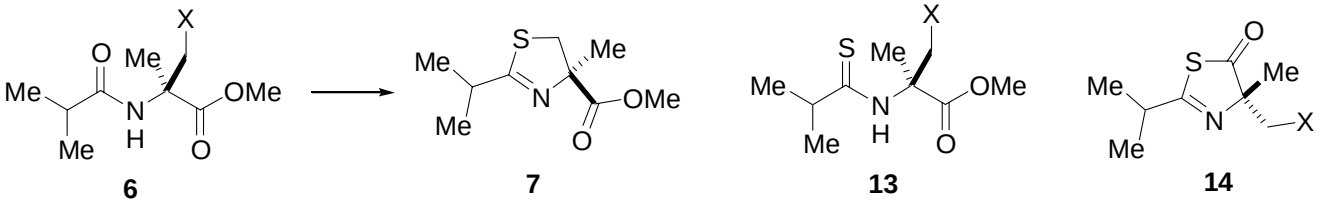
With the model substrates (**6**) in hand, we were able to test a variety of methods for the formation of thiazoline **7** (Table 1). Among the methods selected were thionation of the amide with thionating agents such as $P_2S_4(SC_6H_5)_2$,[10] Lawesson's reagent,[11] and P_4S_{10}, followed by intramolecular attack of the thioamide sulfur and expulsion of a leaving group. Other cyclization conditions involved treatment of cysteine derivatives with oxophilic Lewis Acids such as $TiCl_4$ and PCl_5. The use of PCl_5 for the direct conversion of *S*-protected cysteines to thiazolines has been described with substrates similar to **6**.[12]

For the chloro substrate (**6a**), $P_2S_4(SC_6H_5)_2$, Lawesson's reagent, and P_4S_{10} all gave the desired cyclized product with varying efficiency. Using $P_2S_4(SC_6H_5)_2$ as a thionating agent led to an equal mixture of the desired thiazoline (**7**) along with the thiazolone (**14a**), which results from intramolecular thioamide attack on the methyl ester. The use of Lawesson's reagent gave **7** more selectively, and with P_4S_{10} it was the exclusive product. Thus, P_4S_{10} was found to be superior to the other reagents, giving a higher yield of the desired product without heating. The choice of solvent was important in reactions using P_4S_{10}, with the best results being obtained in acetonitrile.

The iodo substrate (**6b**) was also examined in reactions with P_4S_{10} in acetonitrile. Under these conditions **6b** behaved very differently compared to **6a**, and gave rise to the oxazoline (**12**) as the major product along with only a small amount of the desired thiazoline (**7**). This result was not surprising considering that **12** formed readily during the synthesis of **6b**. The improved leaving group ability of iodide relative to chloride resulted in this premature cyclization occurring much faster then the desired thioamide formation. Therefore, the decreased reactivity of chloride derivatives towards intramolecular cyclization made them a better choice for the formation of thiazoline rings in this study.

It was postulated that the thioethers might undergo the same type of reaction as the halo compounds with P_4S_{10}, in which a mercaptan functions as a leaving group in intramolecular thioamide attack. This notion was supported by some results obtained with more complex models (described in Table 2). However, the *S*-benzyl substrate (**6c**) failed to yield any of the desired thiazoline (**7**) with P_4S_{10}, and instead gave a mixture of the thiazolone (**14c**) and the thioamide (**13c**). The reaction of **6c** with PCl_5 gave only decomposition products, and it proved unreactive with $TiCl_4$.

Table 1



substrate	X	conditions [a]	time (h)	**7,** yield % [b]	**other products** (yield %)
6a	Cl	$P_2S_4(SC_6H_5)_2$	0.5	50	**14a** (50)
		Lawesson's	15	79	**14a** (trace)
		P_4S_{10}	14	86	-
6b	I	P_4S_{10}	20	8	**12** (70)
6c	SBn	P_4S_{10}	24	0	**13c** (29), **14c** (40)
		PCl_5	18	0	-
		$TiCl_4$	3	NR	-
6d	SMe	P_4S_{10} [c]	2	0	**13d** (17), **14d** (70)
		P_4S_{10}	48	0	**14d** (83)
		PCl_5	18	0	-
		$TiCl_4$	3	NR	-
6e	S-4-ClC_6H_4	P_4S_{10}	18	0	**6e** (26)**, 13e** (39), **14e** (35)
6f	disulfide	P_4S_{10}	18	33	-
		$TiCl_4$	3	NR	-
		$TiCl_4$ [d]	3	37	-
6g	SH [e]	P_4S_{10}	18	32	-
		PCl_5	18	47	-
		$TiCl_4$	3	94	-
6h	SAc	P_4S_{10}	48	28	**13h** (14), **14h** (31)
		PCl_5	1	61	-
		$TiCl_4$	3	8	**6h** (69)
6i	STrt	$TiCl_4$	3	58	-

[a] The following conditions were used with each reagent: $P_2S_4(SC_6H_5)_2$ (1.0 equiv.), C_6H_6, 80 °C; Lawesson's (1.05 equiv.), C_6H_6, 80 °C; P_4S_{10} (1 equiv.), MeCN, rt; PCl_5 (2.2 equiv.), CH_2Cl_2, rt; $TiCl_4$ (3 equiv.) in CH_2Cl_2, rt.

[b] NR refers to "no reaction", meaning the starting material was recovered unchanged.

[c] Reaction run at 55 °C

[d] Reaction carried out with one equivalent of C_6H_5SH.

[e] Prepared from **6f** by reduction with Bu_3P and used without further purification.

The *S*-methyl substrate (**6d**) behaved similarly to **6c**, reacting with P_4S_{10} to give a mixture of **13d** and **14d**. The thiazolone (**14d)** became the exclusive product with P_4S_{10} at longer reaction times. The compound (**6d**) gave only decomposition products with PCl_5, and resulted in no reaction with $TiCl_4$.

To further test the use of a mercaptan as a leaving group in intramolecular displacements by a thioamide, an additional change was made in the thioether functionality. Compound (**6e**) was synthesized, which contained a 4-chlorophenyl thioether. The leaving group ability of this functionality was expected to be superior to the other thioethers examined. However, **6e** reacted with P_4S_{10} to give only a mixture of **13e** and **14e** along with recovered starting material.

The disulfide (**6f**) was also tested in thiazoline forming reactions. A low yield of the thiazoline was obtained by the reaction of **6f** with P_4S_{10}. Treatment of **6f** with $TiCl_4$ alone gave no reaction. However, with the addition of one equivalent of thiophenol a modest yield of **7** was obtained. Presumably, thiophenol acts to reduce the disulfide *in situ*, and the mercaptan then cyclizes with $TiCl_4$.

The mercaptan (**6g**) was next examined in cyclization reactions. It was produced from **6f** by reduction with Bu_3P and water, and used in cyclization reactions after a work up, but without purification. The reaction of **6g** with P_4S_{10} resulted in a low yield of **7**. Results were only slightly better with PCl_5. In contrast, the reaction of **6g** with $TiCl_4$ gave the thiazoline in 94% yield over the reduction and cyclization steps. These results suggest that a disulfide protecting strategy for cysteine followed by reduction and cyclodehydration might be useful.

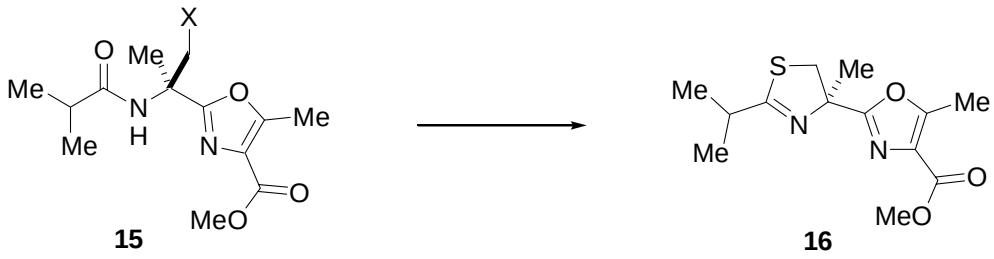
To further improve the leaving group ability of the X-substituent in thionation-cyclization reactions with P_4S_{10}, **6h** was prepared by reduction of the disulfide and acetylation. The thioacetate functionality was intended to function as a better leaving group than the thioethers, and it was hoped that it would better mimic the positive results obtained with chloro substituted **6a**. In reactions with P_4S_{10} the thioacetate (**6h**) did produce a modest yield of the thiazoline (**7**), along with **13h** and **14h**. With PCl_5 **6h** gave a rapid reaction producing the thiazoline in moderate yield. The reaction of **6h** with $TiCl_4$ also proceeded to give thiazoline, but slowly.

Finally, the triphenylmethyl thioether (**6i**) was examined. The direct conversion of similar substrates to thiazolines with $TiCl_4$ has been described.[13] With **6i** the reaction with $TiCl_4$ gave the thiazoline (**7**) in moderate yield.

An Oxazole Containing Model For Thiazoline Formation. The tantazoles and thiangazole contain a terminal oxazole ring in addition to multiple thiazoline rings. In terms of synthetic strategy, it seemed most efficient to carry out thiazoline formation as the last synthetic step in the construction of these molecules. As a consequence of this strategy, the thiazoline forming reactions would need to be carried

out in the presence of this oxazole ring. To explore how the presence of an oxazole ring would affect thiazoline formation, the oxazole containing models **15** were investigated (Scheme 6). Although their synthesis was more involved, these substrates seemed to be better models overall. By adding an oxazole ring they more closely resembled the real system, and even more importantly **15** substitutes an oxazole ring in place of a methyl ester in **6**. This methyl ester often gave rise to the by-product (**14**), which can not form in the case of **15**.

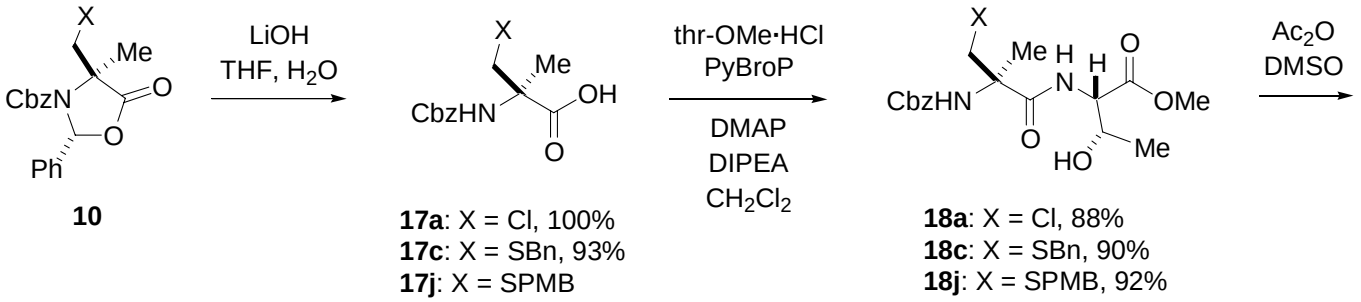
Scheme 6



15 **16**

The synthesis of **15** is described in Scheme 7. In the first step, the oxazolidone (**10**) was fragmented by treatment with lithium hydroxide to release the carboxylic acid (**17**) along with benzaldehyde. This reaction gave access to **17a** and **17c**. For the preparation of **17j** a different strategy, described in Scheme 8, was required due to the inaccessibility of alkylating agents needed to generate **10j**.

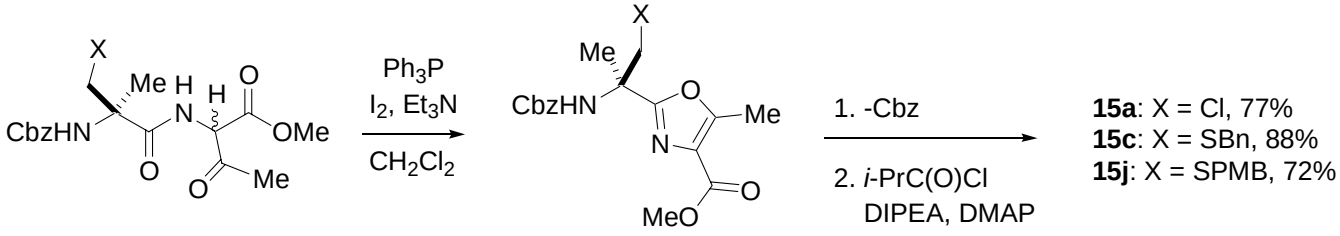
Scheme 7



10

17a: X = Cl, 100%
17c: X = SBn, 93%
17j: X = SPMB

18a: X = Cl, 88%
18c: X = SBn, 90%
18j: X = SPMB, 92%



19a: X = Cl, 70%
19c: X = SBn, 73%
19j: X = SPMB, 72%

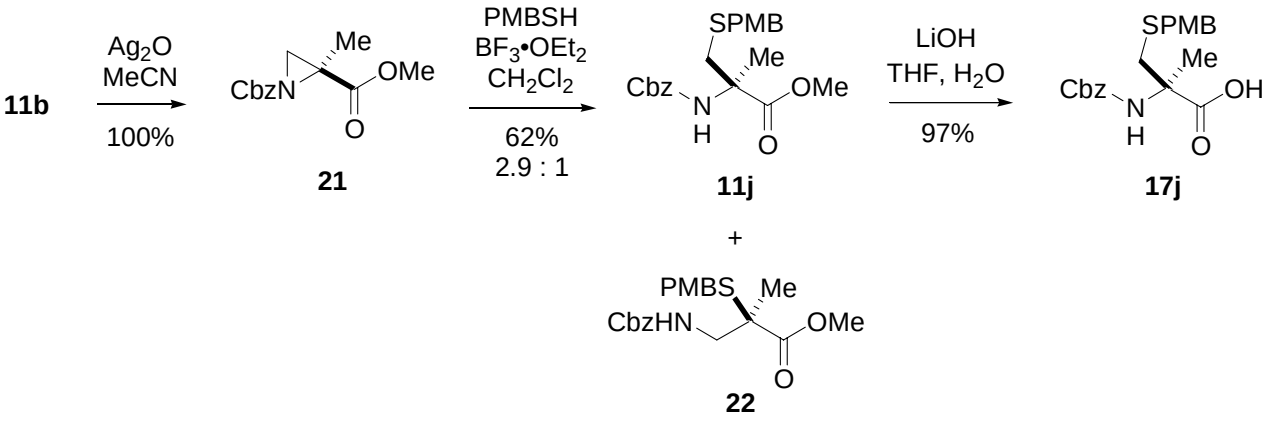
20a: X = Cl, 70%
20c: X = SBn, 92%
20j: X = SPMB, 90%

15a: X = Cl, 77%
15c: X = SBn, 88%
15j: X = SPMB, 72%

The acid (**17**) was next coupled to L-threonine methyl ester using bromo tripyrrolodinophosphonium hexafluorophosphate (PyBroP),[14] to give the dipeptide (**18**). Oxidation of the secondary alcohol of **18** to form the β-keto ester (**19**) failed under a variety of conditions including use of the Dess-Martin reagent, PCC, and standard Moffatt-Swern conditions. Finally, it was found that the Albright-Goldman oxidation[15] using acetic anhydride in DMSO gave good yields of **19**. The cyclodehydration of **19** was carried out using the $Ph_3P/I_2/Et_3N$ conditions developed by Wipf and coworkers,[16] and resulted in rapid formation of the oxazole (**20**) in high yields. Removal of the nitrogen protecting group of **20**, followed by treatment with isobutyryl chloride gave the desired model compounds (**15)**.

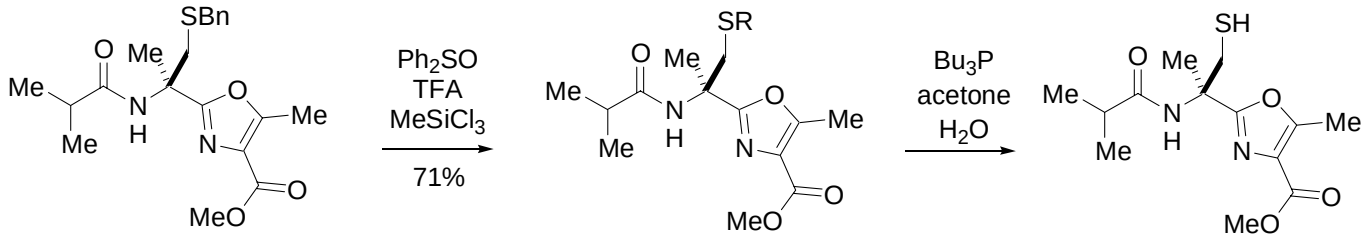
The synthesis of the *S*-PMB protected acid (**17j**) is outlined in Scheme 8. A logical precursor of **17j** was the iodomethyl substituted methyl ester (**11b**). However, numerous attempts to convert **11b** directly to **11j** or **17j** with 4-methoxybenzylmercaptan failed. In these reaction attempts, 4-methoxybenzyl disulfide was the only isolated product. To address this problem an alternate approach was examined in which **11b** was first converted into the aziridine (**21**) in quantitative yield with silver(I) oxide in acetonitrile. This aziridine was then treated with 4-methoxybenzylmercaptan and BF_3•OEt_2 to give the desired ring-opened cysteine derivative (**11j**), along with a smaller amount of the regioisomeric ring-opened product (**22**). The stereochemistry of **22** is not known with complete certainty, and its absolute configuration was tentatively assigned *via* optical rotation by comparison with closely related **11j**. The saponification of **11j** was carried out efficiently with aqueous LiOH and THF to give **17j**.

Scheme 8



In addition to the substrates described in Scheme 7, we were also interested in obtaining the thiol substrate (**15g**). Using a similar approach to that in Scheme 5, **15g** was synthesized as described in Scheme 9. The benzyl thioether (**15c**) was cleaved with diphenyl sulfoxide and methyltrichlorosilane in TFA[17] to give the symmetrical disulfide (**15f**). Reduction of the disulfide bond with tributylphosphine gave the mercaptan (**15g)**, which was used in subsequent reactions without purification.

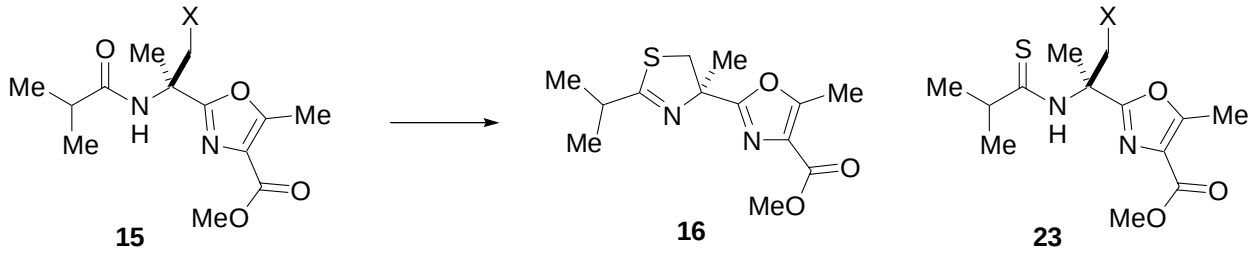
Scheme 9



With the model substrates (**15**) now synthesized, their conversion to the thiazoline (**16)** was examined (Table 2). The same thiazoline forming conditions as were used in Table 1 were used here.

The reaction of the chloro substituted species (**15a**) with P_4S_{10} gave a moderate yield of the desired thiazoline (**16)**, with no other isolable products. Better results were obtained using Lawesson's reagent to carry out thionation, which also led to slow conversion to the thiazoline. The addition of triethylamine following thionation led to rapid conversion of the intermediate thioamide to **16**.

Table 2



substrate	X	reagent [a]	time (h)	**16,** yield %	**other products** (yield %)
15a	Cl	P_4S_{10}	24	56	-
	Cl	Lawesson's [b]	14	74	-
15c	SBn	P_4S_{10} [c]	14	85	-
		Lawesson's	14	0	**23c** (92)
		$P_2S_4(SC_6H_5)_2$	1	0	**23c** (96)
		PCl_5	16	42	-
23c	SBn	P_4S_{10} [c]	14	62	-
15g	SH	$TiCl_4$	4	73	-
15j	SPMB	P_4S_{10} [c]	14	66	-
		PCl_5	15	72	-

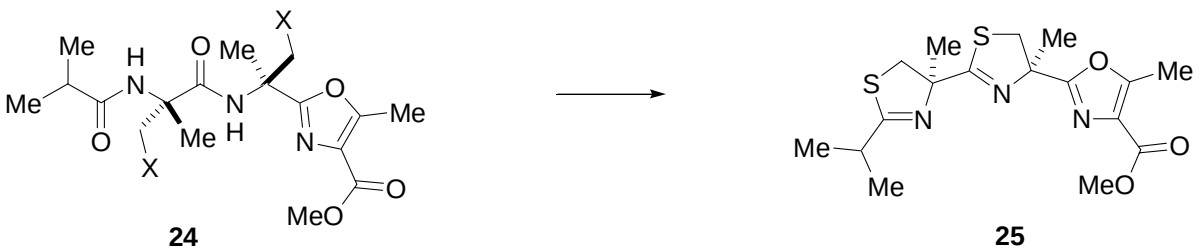
[a] The following conditions were used with each reagent: $P_2S_4(SC_6H_5)_2$ (1.0 equiv.), C_6H_6, 80 °C; Lawesson's (1.05 equiv.), C_6H_6, 55 °C; P_4S_{10} (1 equiv.), MeCN, rt; PCl_5 (2.2 equiv.), CH_2Cl_2, rt; $TiCl_4$ (3 equiv.) in CH_2Cl_2, rt.
[b] Following reaction with Lawesson's reagent, excess Et_3N was added and the reaction heated 2 h longer.
[c] Reaction heated at 55 °C

Some interesting results were obtained in the reactions of **15c**. In its reaction with P_4S_{10}, **15c** somewhat unexpectedly gave a good yield of the thiazoline (**16**). In addition to functioning as a thionating agent in the conversion of **15c** to its thioamide, the Lewis acidic P_4S_{10} may also be binding to the thioether and activating the molecule for cyclization. It is also interesting to note that the reaction of **15c** with Lawesson's reagent stopped selectively at the thioamide stage, giving a 92% yield of this compound with no isolable amount of the cyclized species. The same was true when $P_2S_4(SC_6H_5)_2$ was used as the thionating agent, with **23c** produced selectively in 96% yield. Treatment of this intermediate thioamide (**23c**) with P_4S_{10} leads to the thiazoline. From these results it appears that the thioamide is likely an intermediate in the conversion of **15c** to **16** with P_4S_{10}. It is also clear that P_4S_{10} is able to activate the thioether of **23** towards cyclization in a way that Lawesson's reagent and $P_2S_4(SC_6H_5)_2$ do not. The amide (**15c**) was also found to give **16** in moderate yield when combined with PCl_5. This is in contrast to the reaction of the *S*-benzyl ether (**6c**) with PCl_5 in which only decomposition was observed.

The *S*-4-methoxybenzyl protected derivative (**15j**) was also examined. This sulfur protecting group was more electron-rich, and more labile under acidic and Lewis acidic conditions than the *S*-benzyl derivative (**15c**). This property didn't directly translate into a better yield of thiazoline in the reaction of **15j** with P_4S_{10}, which gave the desired product in 66% yield. However, in the reaction of **15j** with PCl_5, a significant improvement in the yield of **16** relative to **15c** was observed. With **15j** and PCl_5 the desired thiazoline was obtained in 72% yield.

Advanced Models For Thiazoline Formation. The final model system examined is shown in Scheme 10. The model (**24**) contains an oxazole ring and two cysteine residues for the formation of two thiazoline rings in **25**. This model addresses perhaps the most important issue in the synthesis of tantazoles and tantazole-like molecules: the simultaneous formation of multiple thiazoline rings in one step.

Scheme 10

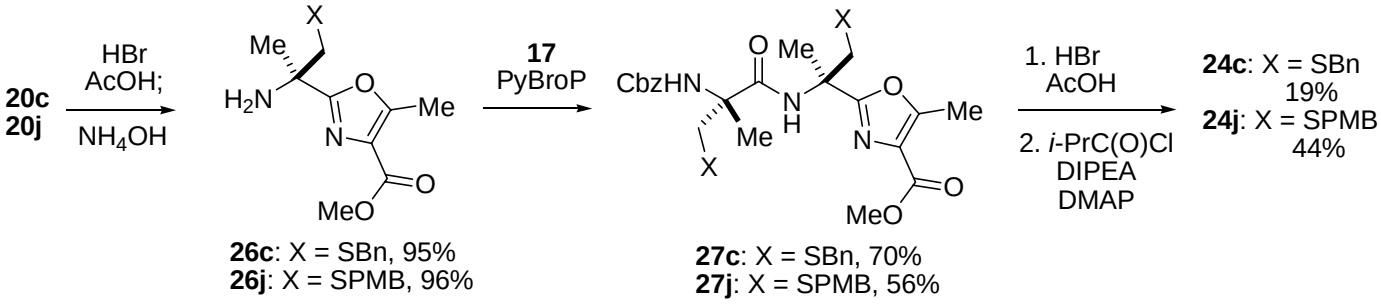


24 **25**

The synthesis of **24** is described in Scheme 11. The Cbz-protecting group of **20** was first removed with HBr in acetic acid, and the resulting hydrobromide salt neutralized to give the free base (**26**). This amine was then coupled with a molecule of **17** to give **27**. Finally, the Cbz-group of **27** was removed and the resulting amine treated with isobutyryl chloride to give **24**. The yields in this final deprotection and

aceylation sequence were unoptimized. Attempts were made to synthesize the chloro-analog (**24a**). However, difficulties were encountered with this substrate during the coupling step in going from **26a** to **27a**. Low yields (~26%) were obtained in this step, with decomposition of **26a** being a significant problem.

Scheme 11



26c: X = SBn, 95%
26j: X = SPMB, 96%

27c: X = SBn, 70%
27j: X = SPMB, 56%

With **24c** and **24j** now synthesized, conditions were examined in an attempt to close the two thiazoline rings simultaneously. These results are described in Table 3.

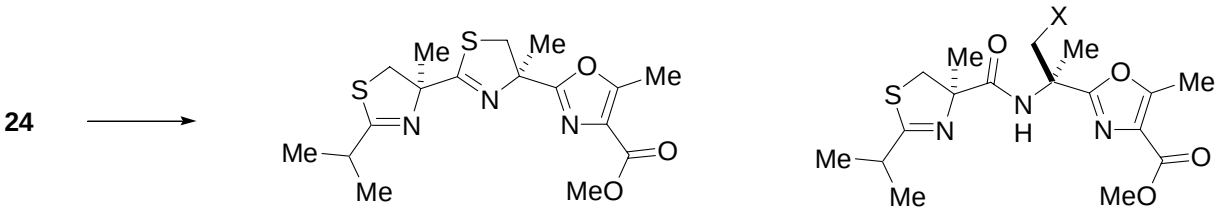
In reactions with P_4S_{10} **24c** yielded **28c**, in which only the outer thiazoline ring has formed. The inner amide in **24** is much more hindered then the other amide, and under the reaction conditions it was not thionated. This result was confirmed by mass spectrometery. In an attempt to convert the inner amide to a thioamide, **28c** was resubmitted to reaction with P_4S_{10} at higher temperatures. However, this failed to produce **25**, and resulted only in slow decomposition of **28c**. When subjected to more aggressive thionating conditions with $P_2S_4(SC_6H_5)_2$ in refluxing benzene, the fragmentation product (**14c**) was observed as the major product.

The *S*-4-methoxybenzyl protected derivative (**24j**) behaved similarly with P_4S_{10}, giving the outer ring closure product (**28j**). Reactions of **24j** with PCl_5 and $TiCl_4$ led only to decomposition products. A variety of other Lewis acids were also surveyed for this transformation, including $POCl_3$, $SOCl_2$, $(ClCO)_2$, MsCl, and TMSBr. Unfortunately, none of these were able to successfully convert **24j** into **25**.

CONCLUSIONS

The identification of new methods for the simultaneous closure of thiazoline rings in the tantazoles, mirabzoles and thiangazole remains a significant challenge. Several methods were found to be useful for the formation of a single thiazoline ring. These methods included the reaction of 2-halomethylalanines or certain 2-methylcysteines with P_4S_{10} in acetonitrile, and the reaction of certain 2-methylcysteines with PCl_5 or $TiCl_4$. Although successful in generating thiazolines **7** and **16**, problems were encountered in

Table 3



25 **28**

substrate	X	reagent [a]	time, h	temp, °C	**products** (yield %) [b]
24c	SBn	P_4S_{10}	24	55	**28c** (68)
		$P_2S_4(SC_6H_5)_2$	4	80	**14c** (95)
28c	SBn	P_4S_{10}	14	80	NR
24j	SPMB	P_4S_{10}	48	rt	**28j** (30)
		PCl_5	1	rt	-
		$TiCl_4$	16	rt	-
		$POCl_3$	2	rt	NR
		$POCl_3$/DMF	18	rt	-
		$SOCl_2$	24	rt	-
		$(ClCO)_2$	24	rt	-
		MsCl	16	rt	NR
		TMSBr	16	rt	-

[a] The following conditions were used with each reagent: P_4S_{10} (2 equiv.), MeCN; $P_2S_4(SC_6H_5)_2$ (2 equiv.), C_6H_6; PCl_5 (2.2 equiv.), CH_2Cl_2; $TiCl_4$ (6 equiv.), CH_2Cl_2; $POCl_3$ (6 equiv.), CH_2Cl_2 or DMF; $SOCl_2$ (6 equiv.), CH_2Cl_2; $(COCl)_2$ (6 equiv.), CH_2Cl_2; MsCl (6 equiv.), CH_2Cl_2; TMSBr (6 equiv.), CH_2Cl_2.
[b] NR refers to "no reaction", meaning the starting material was recovered unchanged.

applying these methods to the formation of very hindered thiazolines such as those found in **25** and in the interior rings of the tantazoles, and related natural products. Future work will focus on the reduction of disulfide protected 2-methylcysteines to thiols followed by cyclodehydration with $TiCl_4$. This strategy was used successfully in conversion of **6f** and **15f** into **6g** and **15g** respectively, followed by cyclization to the thiazolines (**7** and **16**).

EXPERIMENTAL

General Experimental. Compounds (**10c**, **11c** and **17c**) were synthesized as previously reported.[b] Benzene, hexamethylphosphoramide (HMPA), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU), diisopropylethylamine, and triethylamine were dried by distillation from CaH_2. Tetrahydrofuran (THF) was dried by distillation from sodium/benzophenone. Methylene chloride was

purchased anhydrous and stored over 4 Å molecular sieves. Acetonitrile was purchased anhydrous and used as received. Brine refers to saturated aqueous NaCl solution. Flash chromatography was performed with silica gel 60, 230-400 mesh. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively.

(*R*)-3-Chloro-2-isobutyrylamino-2-methylpropionic acid methyl ester (6a). Compound (**11a**) (0.6012 g, 2.1041 mmol) was dissolved in CH_2Cl_2 (28 mL), and a 30% solution of HBr in AcOH (14 mL) was added, with stirring. After 1 h at rt, volatile components were removed under vacuum to yield the crude hydrobromide salt. This compound was mixed with CH_2Cl_2 (10.5 mL) under N_2 and cooled to −78 °C. Diisopropylethylamine (1.82 mL, 10.45 mmol) was added dropwise, with stirring, followed by isobutyryl chloride (0.66 mL, 6.33 mmol), and a solution of DMAP (0.257 g, 2.104 mmol) in CH_2Cl_2 (1.5 mL). After 1 h the solution was warmed to 0 °C and quenched by addition of H_2O (6 mL). The layers were separated and the organic phase washed with brine, dried over $MgSO_4$, filtered, and solvent removed under vacuum. The product was purified by flashing through a plug of silica gel to remove baseline impurities. The product was obtained as white needles, and was recrystallized from hexane (0.3490 g, 75%): TLC R_f 0.34 (3:1 hexane/EtOAc); mp 76-76.5 °C; $[\alpha]^{25}_{D}$ = +16.6º (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, δ ppm) 6.35 (br s, 1 H), 4.40 (d, *J* = 11.2 Hz, 1 H), 4.01 (d, *J* = 11.2 Hz, 1 H), 3.82 (s, 3 H), 2.42 (heptet, *J* = 7.2 Hz, 1 H), 1.64 (s 3 H), 1.22 (d, *J* = 7.2 Hz, 3 H), 1.18 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 176.6, 172.4, 60.5, 53.0, 46.6, 35.6, 21.5, 19.3, 19.2; FAB HRMS *m/z* (M+H) calcd 222.0897, found 222.0901. Anal. Calcd for $C_9H_{16}NO_3Cl$: C, 48.76; H, 7.27; N, 6.32. Found: C, 49.06; H, 7.44; N, 6.08.

(*R*)-3-Iodo-2-isobutyrylamino-2-methylpropionic acid methyl ester (6b). Compound (**11b**) (0.4266 g, 1.131 mmol) was dissolved in CH_2Cl_2 (15 mL), and a 30% solution of HBr in AcOH (7.5 mL) was added, with stirring. After 2 h at rt, volatile components were removed under vacuum to yield the crude hydrobromide salt. This compound was dissolved in CH_2Cl_2 (5.7 mL) under N_2 and cooled to −78 °C. A solution of DMAP (0.1382 g, 1.131 mmol) in CH_2Cl_2 (0.75 mL) was added dropwise, with stirring, followed by diisopropylethylamine (0.985 mL, 5.655 mmol), and isobutyryl chloride (0.355 mL, 3.393 mmol). The solution was stirred for 2 h at −78 °C and then quenched by addition of 10% aq. $KHSO_4$ (5 mL) at −78 °C with vigorous stirring and then allowed to warm to rt. The layers were separated and the aqueous phase extracted once with CH_2Cl_2. The combined CH_2Cl_2 layers were dried over $MgSO_4$, filtered, concentrated, and the crude product purified by flash chromatography (3:1 hexane/EtOAc), giving the product as a yellow microcrystalline solid (0.281 g, 79%): TLC R_f 0.31 (3:1 hexane/EtOAc); mp 67-68 °C; $[\alpha]^{25}_{D}$ = +24.9º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}, CCl_4) 3314, 2973, 1739, 1671, 1524, 1447, 1269, 1230, 1111; ^{1}H NMR ($CDCl_3$, δ ppm) 6.38 (br s, 1 H), 4.23 (d, *J* = 10.4 Hz, 1 H), 3.83 (s, 3

H), 3.74 (d, *J* = 10.4 Hz, 1 H), 2.42 (heptet, *J* = 6.8 Hz, 1 H), 1.74 (s, 3 H), 2.00 (d, *J* = 6.8 Hz, 3 H), 1.18 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 176.4, 171.9, 59.7, 53.3, 35.7, 22.8, 19.5, 19.3, 12.0; FAB LRMS *m/z* (M+H) 314, (M – I) 186; Anal. Calcd for $C_9H_{16}NO_3I$: C, 34.52; H, 5.15; N, 4.47. Found: C, 34.67; H, 5.28; N, 4.29.

(*R*)-3-Benzylsulfanyl-2-isobutyrylamino-2-methylpropionic acid methyl ester (6c). Following the procedure used for synthesis of **6a**, the product was obtained as a yellow oil (91%): TLC R_f 0.25 (3:1 hexane/EtOAc); $[\alpha]^{25}_D$ = +2.2º (*c* 0.51, $CHCl_3$); IR (NaCl, cm^{-1}) 3316, 2969, 1739, 1657, 1527, 1453, 1225; ^{1}H NMR ($CDCl_3$, δ ppm) 7.32-7.21 (m, 5 H), 6.42 (br s, 1 H), 3.70 (s, 3 H), 3.67 (d, *J* = 13.6 Hz, 1 H), 3.63 (d, *J* = 13.6 Hz, 1 H), 3.44 (d, *J* = 13.6 Hz, 1 H), 3.01 (d, *J* = 13.6 Hz, 1 H), 2.36 (heptet, *J* = 6.8 Hz, 1 H), 1.57 (s, 3 H), 1.15 (d, *J* = 6.8 Hz, 3 H), 1.14 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 176.3, 173.7, 138.1, 128.7, 128.4, 127.0, 60.3, 52.7, 37.4, 37.3, 35.7, 23.0, 19.3; FAB HRMS *m/z* (M+H) calcd 310.1477, found 310.1484. Anal. Calcd for $C_{16}H_{23}NO_3S$: C, 62.11; H, 7.49; N, 4.53. Found: C, 62.07; H, 7.59; N, 4.59.

(*R*)-2-Isobutyrylamino-2-methyl-3-methylsulfanylpropionic acid methyl ester (6d). Following the procedure used for synthesis of **6a**, the product was obtained as an oil that crystallized upon standing (88%): TLC R_f 0.31 (3:1 hexane/EtOAc); mp 48-49 °C; $[\alpha]^{25}_D$ = +24.3º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3310, 2971, 1738, 1656, 1535, 1284, 1230, 1117; ^{1}H NMR ($CDCl_3$, δ ppm) 6.48 (br s, 1 H), 3.76 (s, 3 H), 3.50 (d, *J* = 13.6 Hz, 1 H), 3.06 (d, *J* = 13.6 Hz, 1 H), 2.40 (heptet, *J* = 6.8 Hz, 1 H), 2.09 (s, 3 H), 1.63 (s, 3 H), 1.17 (d, *J* = 6.8 Hz, 1 H), 1.14 (d, *J* = 6.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, δ ppm) 176.3, 173.8, 60.6, 52.7, 40.0, 35.7, 34.5, 23.0, 19.3, 19.2, 16.9; FAB LRMS *m/z* (M+H) 234, (M − SMe) 186, (M − *i*-PrC(O)NH_2) 146; Anal. Calcd for $C_{10}H_{19}NO_3S$: C, 51.48; H, 8.21; N, 6.00; S, 13.74. Found: C, 51.79; H, 8.56; N, 5.95; S, 13.89.

(*R*)-3-(4-Chlorophenylsulfanyl)-2-isobutyrylamino-2-methylpropionic acid methyl ester (6e). Following the procedure used for synthesis of **6a**, the product was obtained as white needles (95%): TLC R_f 0.28 (3:1 hexane/EtOAc); mp 68.5-69 °C; $[\alpha]^{25}_D$ = +44.8º (*c* 0.105, $CHCl_3$); IR (NaCl, cm^{-1}) 3304, 2971, 1739, 1652, 1538, 1477, 1095; ^{1}H NMR ($CDCl_3$, δ ppm) 7.31-7.22 (AA'XX' pattern, 4 H), 6.39 (br s, 1 H), 3.99 (d, *J* = 13.6 Hz, 1 H), 3.64 (s, 3 H), 3.45 (d, *J* = 13.6 Hz, 1 H), 2.21 (heptet, *J* = 7.2 Hz, 1 H), 1.65 (s, 3 H), 1.06 (d, *J* = 7.2 Hz, 3 H), 1.05 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 176.2, 173.5, 134.1, 132.5, 131.8, 128.8, 60.6, 52.8, 39.7, 35.6, 23.1, 19.2, 19.1; FAB LRMS *m/z* (M+H) 330 (M − *i*-PrC(O)NH) 242; Anal. Calcd for $C_{15}H_{20}NO_3ClS$: C, 54.62; H, 6.11; N, 4.25. Found: C, 54.51; H, 6.10; N, 4.37.

(*R*,*R*)-2-Isobutyrylamino-3-(2-isobutyrylamino-2-methoxycarbonylpropyldisulfanyl)-2-methylpropionic acid methyl ester (6f). Compound (**6c**) (2.3451 g, 7.579 mmol) was mixed with Ph_2SO (7.666 g, 37.898 mmol), TFA (48.5 mL), and $MeSiCl_3$ (17.6 mL, 149.9 mmol), with stirring. Within 1 h a liquid-liquid phase separation occurred. After 1 h, volatile components were removed in a stream of N_2 followed by vacuum. The resulting residue was mechanically mixed with enough 10% aq. Na_2CO_3 to make the resulting mixture basic. This solid-liquid mixture was extracted four times with ether, and the combined ether layers washed twice with brine, and dried over $MgSO_4$. Filtering and concentration of the filtrate gave a cloudy oil which was purified by flash chromatography (3:1→1:1→1:2 hexane/EtOAc). Product was obtained as white needles (1.186 g, 72%): TLC R_f 0.29 (2:1 hexane/ether); mp 103-105 °C; $[\alpha]^{25}_D$ = +124.7º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3303, 2971, 1739, 1656, 1530; ^{1}H NMR ($CDCl_3$, δ ppm) 6.56 (br s, 1 H), 3.71 (s, 3 H), 3.61 (d, *J* = 14.0 Hz, 1 H), 3.26 (d, *J* = 14.0 Hz, 1 H), 2.36 (heptet, *J* = 6.8 Hz, 1 H), 1.53 (s, 3 H), 1.09 (d, *J* = 6.8 Hz, 3 H), 1.08 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 176.5, 173.4, 59.8, 52.8, 44.6, 35.6, 23.0, 19.3, 19.2; FAB LRMS *m/z* (M+H) 437, (M − $C_9H_{16}NO_3S$) 218; Anal. Calcd for $C_{18}H_{32}N_2O_6S_2$: C, 49.52; H, 7.39; N, 6.42; S, 14.69. Found: C, 49.18; H, 7.45; N, 6.38; S, 14.65.

(*R*)-2-Isobutyrylamino-3-mercapto-2-methylpropionic acid methyl ester (6g). Disulfide (**6f**) (0.4293 g, 0.9833 mmol) was dissolved in acetone (34 mL) under argon, and H_2O (8.5 mL) added, followed by Bu_3P (0.269 mL, 1.080 mmol, 1.1 equiv). After stirring 15 min at rt the reaction was complete, and acetone was evaporated in a stream of argon. The resulting mixture was extracted three times with CH_2Cl_2, and the combined CH_2Cl_2 layers dried over Na_2SO_4 under argon. This solution was decanted and transferred by cannula to another flask under argon and the solvent evaporated to give the crude thiol as a yellow oil. This compound was used in subsequent steps without further purification.

(*R*)-3-Acetylsulfanyl-2-isobutyrylamino-2-methylpropionic acid methyl ester (6h). Disulfide (**6f**) (0.1470 g, 0.3367 mmol) was reduced to **6g** as described and dissolved in CH_2Cl_2 (2.5 mL). The solution was cooled to 0 °C and DIPEA (176 μL, 1.010 mmol) was added followed by Ac_2O (120 μL, 1.684 mmol), with stirring. After 30 min, the reaction was complete, and the reaction mixture concentrated at rt and loaded directly onto a flash column (3:1 hexane/EtOAc). The product was isolated as white needles (0.1538 g, 87%): TLC R_f 0.10 (3:1 hexane/EtOAc); mp 88-89 °C; $[\alpha]^{25}_D$ = +36.5º (*c* 1.10, $CHCl_3$); IR (NaCl, cm^{-1}, CCl_4) 3312, 2969, 1739, 1698, 1505, 1446, 1222, 1116; ^{1}H NMR ($CDCl_3$, δ ppm) 6.46 (br s, 1 H), 3.65 (s, 3 H), 3.55 (d, *J* = 14.0 Hz, 1 H), 3.50 (d, *J* = 14.0 Hz, 1 H), 2.28 (heptet, *J* = 7.2 Hz, 1 H), 2.23 (s, 3 H), 1.46 (s, 3 H), 1.04 (d, *J* = 7.2 Hz, 6 H); ^{13}C NMR ($CDCl_3$, δ ppm) 195.0, 176.5, 173.0, 59.1, 52.6, 35.3, 34.8, 30.2, 22.2, 19.2, 19.1; FAB LRMS *m/z* (M+H) 262; Anal. Calcd for $C_{11}H_{19}NO_4S$: C, 50.55; H, 7.33; N, 5.36. Found: C, 50.75; H, 7.43; N, 5.25.

(*R*)-2-Isobutyrylamino-2-methyl-3-tritylsulfanylpropionic acid methyl ester (6i). Disulfide (**6f**) (59.3 mg, 0.1358 mmol) was reduced to **6g** as described and dissolved in CH_2Cl_2 (0.5 mL) under argon. To this solution was added triphenylmethanol (74.3 mg, 0.2988 mmol) followed by TFA (0.5 mL), which resulted in development of a red color. After stirring 30 min, solvents were removed under vacuum, and the residue treated with 10% aq. Na_2CO_3, giving a sticky white residue. Extraction with ether, drying over Na_2SO_4, filtering, and concentration gave a colorless residue. Purification by flash chromatography gave the product as a white solid (85.1 mg, 68%): TLC R_f 0.27 (3:1 hexane/EtOAc); mp 53-55 °C; $[\alpha]^{25}_D$ = −8.2° (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3406, 3058, 2969, 1741, 1664, 1493, 1446, 1291; ^{1}H NMR ($CDCl_3$, δ ppm) 7.43-7.19 (m, 18 H), 6.08 (br s, 1 H), 3.66 (s, 3 H), 3.05 (d, *J* = 11.7 Hz, 1 H), 2.67 (d, *J* = 11.7 Hz, 1 H), 2.33 (heptet, *J* = 6.9 Hz, 1 H), 1.42 (s, 3 H), 1.17 (d, *J* = 6.9 Hz, 3 H), 1.15 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 176.1, 173.5, 144.5, 129.4, 127.8, 126.7, 66.3, 58.8, 52.7, 37.8, 35.6, 23.0, 19.4, 19.3; FAB LRMS *m/z* (M+^{7}Li) 468.3, (Trt+) 243.1; Anal. Calcd for $C_{28}H_{31}NO_3S$: C, 72.85; H, 6.77; N, 3.03. Found: C, 72.66; H, 6.95; N, 2.96.

(*R*)-2-Isopropyl-4-methyl-4,5-dihydrothiazole-4-carboxylic acid methyl ester (7). Typical procedures for the conversion of **6** to **7**, **13**, and **14** are listed below.

A. Using $P_2S_2(SPh)_2$: Compound (**6**) (1 mol equiv.) was dissolved in C_6H_6 (5 mL/mmol) and $P_2S_2(SC_6H_5)_2$ (1 mol equiv.) was added. The mixture was heated in a resealable tube at 80 °C, with stirring, and monitored by TLC. When the reaction was complete, the mixture was poured into sat. aq. $NaHCO_3$, stirred, and extracted twice with ether. The combined ether layers were washed with brine, dried over $MgSO_4$, filtered, and purified by flash chromatography.

B. Using Lawesson's Reagent: Compound (**6**) (1 mol equiv.) was dissolved in C_6H_6 (5 mL/mmol) and Lawesson's reagent (1.05 mol equiv.) was added. The mixture was heated in a resealable tube at the indicated temperature, with stirring, and monitored by TLC. When the reaction was complete, triethylamine was added, and the crude mixture purified directly by flash chromatography.

C. Using P_4S_{10}: Compound (**6**) (1 mol equiv.) was dissolved in MeCN (6 mL/mmol) and P_4S_{10} (1 mol equiv.) was added. The mixture was either heated in a resealable tube or stirred at rt as indicated, and monitored by TLC. When the reaction was complete, the mixture was poured into sat. aq. $NaHCO_3$, stirred, and extracted twice with ether. The combined ether layers were washed with brine, dried over $MgSO_4$, filtered, and purified by flash chromatography.

D. Using PCl_5: Compound (**6**) (1 mol equiv.) was dissolved in CH_2Cl_2 (10 mL/mmol) and PCl_5 (2.5 mol equiv.) was added. The solution was stirred at rt and monitored by TLC. When the reaction was complete, the mixture was poured into sat. aq. $NaHCO_3$, stirred, and extracted twice with ether. The

combined ether layers were washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography.

E. Using $TiCl_4$: Compound (**6**) (1 mol equiv.) was dissolved in CH_2Cl_2 (3.6 mL/mmol) under N_2, and 1 M $TiCl_4$ in CH_2Cl_2 (3 mol equiv.) was added, with stirring. The solution was stirred at rt and monitored by TLC. When the reaction was complete, the mixture was poured into 10% aq. $NaHCO_3$, stirred, and extracted twice with CH_2Cl_2. The combined CH_2Cl_2 layers were washed dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography.

7: The compound is a clear colorless liquid. Spectral data match the published data for this compound:[6c] TLC R_f 0.40 (3:1 hexane/EtOAc); IR (NaCl, cm^{-1}) 2970, 1738, 1619, 1288, 1200, 1126; ^1H NMR ($CDCl_3$, δ ppm) 3.77 (s, 3 H), 3.70 (d, *J* = 11.6 Hz, 1 H), 3.10 (d, *J* = 11.6 Hz, 1 H), 2.85 (heptet, *J* = 6.8 Hz, 1 H), 1.50 (s, 3 H), 1.20 (d, *J* = 6.8 Hz, 3 H), 1.19 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 177.9, 173.9, 83.7, 52.7, 41.0, 33.9, 23.8, 21.1, 21.0; FAB LRMS *m/z* (M+H) 202.1; Anal. Calcd for $C_9H_{15}NO_2S$: C, 53.70; H, 7.51; N, 6.96. Found: C, 53.47; H, 7.79; N, 6.77.

(*R*)-4-Chloromethyl-4-methyl-5-oxo-2-phenyloxazolidine-3-carboxylic acid benzyl ester (10a). THF (36 mL), DMPU (6 mL), and 1 M LHMDS solution in THF (7.60 mL, 7.60 mmol) were mixed under an N_2 atmosphere at rt, with stirring. This solution was cooled to −78 °C and a solution of **8** (2.297 g, 7.379 mmol) in THF (10 mL) was added dropwise, with stirring. After stirring an additional 30 min, a solution of chloroiodomethane (**9a**) (1.60 mL, 22.1 mmol, 3 equiv.) in THF (4 mL) was added dropwise. After stirring at −78 °C for 90 min the reaction was complete, and was worked up by warming to 0 °C and quenching with sat. aq. NH_4Cl (46 mL). The mixture was extracted with ether (2 X 20 mL), and the combined ether extracts washed with sat. aq. NH_4Cl (10 mL), H_2O (2 X 10 mL), and brine (10 mL). The solution was dried over $MgSO_4$, filtered, and solvent removed under reduced pressure to give an oil which was purified by flash chromatography (4:1 hexane/ether). Product was obtained as a clear colorless oil (2.234g, 84%): TLC R_f 0.24 (4:1 hexane/ether); $[\alpha]^{25}_D$ = +78.5º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3036, 1800, 1715, 1405, 1347, 1022; ^1H NMR ($CDCl_3$, δ ppm) 2.3:1 mixture of rotomers, major rotomer: 7.46-7.21 (m, 8 H), 6.89 (d, *J* = 6.8 Hz, 2 H), 6.51 (s, 1 H), 5.08 (d, *J* = 12.0 Hz, 1 H), 5.01 (d, *J* = 12.0 Hz, 1 H), 4.59 (d, *J* = 11.2 Hz, 1 H), 3.87 (d, *J* = 11.2 Hz, 1 H), 1.85 (s, 3 H); minor rotomer: 7.46-7.21 (m, 10 H), 6.60 (s, 1 H), 5.32 (d, *J* = 12.0 Hz, 1 H), 5.08 (d, *J* = 12.0 Hz, 1 H), 4.12 (d, *J* = 11.2 Hz, 1 H), 3.84 (d, *J* = 11.2 Hz, 1 H), 1.73 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 172.5, 172.1, 152.5, 151.7, 136.4, 136.0, 135.0, 130.0, 128.7, 128.4, 128.3, 128.1, 127.6, 126.9, 126.8, 90.3, 68.2, 67.5, 64.1, 63.5, 47.6, 45.9, 22.5, 21.6; FAB HRMS *m/z* (M+H) calcd 360.1003, found 360.1006. Anal. Calcd for $C_{19}H_{18}NO_4Cl$: C, 63.43; H, 5.04; N 3.89. Found: C, 63.44; H, 5.18; N, 3.73.

(*R*)-4-Iodomethyl-4-methyl-5-oxo-2-phenyloxazolidine-3-carboxylic acid benzyl ester (10b). Following the procedure used for synthesis of **10a**, but using HMPA in place of DMPU, the product was obtained as a clear colorless oil that slowly crystallized (76%): TLC R_f 0.24 (4:1 hexane/ether); mp 52-53 °C; $[\alpha]^{27}_D$ = +107.0º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3036, 1803, 1714, 1404, 1347, 1022; ^1H NMR ($CDCl_3$, δ ppm) 2.3:1 mixture of rotomers, major rotomer: 7.47-7.22 (m, 8 H), 6.94 (d, *J* = 8.0 Hz, 2 H), 6.58 (s, 1 H), 5.08 (d, *J* = 12.0 Hz, 1 H), 5.05 (d, *J* = 12.0 Hz, 1 H), 4.35 (d, *J* = 12.0 Hz, 1 H), 3.65 (d, *J* = 12.0 Hz, 1 H), 1.97 (s, 3 H); minor rotomer: 7.47-7.22 (m, 10 H), 6.66 (s, 1 H), 5.32 (d, *J* = 12.0 Hz, 1 H), 5.08 (d, *J* = 12.0 Hz, 1 H), 3.85 (d, *J* = 12.0 Hz, 1 H), 3.63 (d, *J* = 12.0 Hz, 1 H), 1.85 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 172.8, 172.4, 152.1, 151.5, 136.3, 135.8, 135.0, 134.8, 130.0, 128.8, 128.7, 128.6, 128.3, 128.1, 127.7, 126.9, 126.8, 90.0, 68.3, 67.5, 63.4, 62.9, 23.7, 22.6, 10.6, 9.0; FAB HRMS *m/z* (M+H) calcd 452.0359, found 452.0353. Anal. Calcd for $C_{19}H_{18}NO_4I$: C, 50.57; H, 4.02; N, 3.10. Found: C, 50.67; H, 4.09; N, 2.90.

(*R*)-4-Methyl-4-methylsulfanylmethyl-5-oxo-2-phenyloxazolidine-3-carboxylic acid benzyl ester (10d). Following the procedure used for synthesis of **10a**, the product was obtained as a yellow oil (80%): TLC R_f 0.20 (4:1 hexane/ether); $[\alpha]^{25}_D$ = +105.9º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3035, 2924, 1796, 1713, 1407, 1346, 1272, 1023; ^1H NMR ($CDCl_3$, δ ppm) 2:1 mixture of rotomers, major rotomer: 7.44-7.19 (m, 8 H), 6.87 (d, *J* = 6.8 Hz, 1 H), 6.55 (s, 1 H), 5.02 (d, *J* = 12.0 Hz, 1 H), 4.97 (d, *J* = 12.0 Hz, 1 H), 3.78 (d, *J* = 14.0 Hz, 1 H), 2.96 (d, *J* = 14.0 Hz, 1 H), 2.15 (s, 3 H), 1.84 (s, 3 H); minor rotomer: 7.44-7.19 (m, 10 H), 6.61 (s, 1 H), 5.27 (d, *J* = 12.0 Hz, 1 H), 5.04 (d, *J* = 12.0 Hz, 1 H), 3.36 (d, *J* = 14.0 Hz, 1 H), 2.93 (d, *J* = 14.0 Hz, 1 H), 2.06 (s, 3 H), 1.73 (s, 3 H). ^{13}C NMR ($CDCl_3$, δ ppm) 174.2, 173.8, 152.6, 151.8, 136.9, 136.4, 135.2, 128.7, 128.6, 128.3, 128.0, 127.7, 126.9, 126.8, 90.4, 67.9, 67.3, 65.8, 64.0, 63.5, 41.7, 39.9, 24.4, 23.5, 16.8, 15.3; FAB LRMS *m/z* (M+H) 372, (M − CH_2SCH_3) 310. Anal. Calcd for $C_{20}H_{21}NO_4S$: C, 64.67; H, 5.70; N, 3.77; S, 8.63. Found: C, 64.50; H, 5.88; N, 3.95; S, 8.93.

(*R*)-4-(4-Chlorophenylsulfanylmethyl)-4-methyl-5-oxo-2-phenyloxazolidine-3-carboxylic acid benzyl ester (10e). Following the procedure used for synthesis of **10a**, the product was obtained as a clear colorless oil (69%): TLC R_f 0.17 (4:1 hexane/ether); $[\alpha]^{25}_D$ = +69.0º (*c* 2.94, $CHCl_3$); IR (NaCl, cm^{-1}) 3036, 2936, 1798, 1713, 1407, 1347, 1024; ^1H NMR ($CDCl_3$, δ ppm) 2:1 mixture of rotomers, major rotomer: 7.44-7.16 (m, 8 H), 6.73 (d, *J* = 7.2 Hz, 2 H), 6.33 (s, 1 H), 4.86 (d, *J* = 12.0 Hz, 1 H), 4.48 (d, *J* = 12.0 Hz, 1 H), 4.21 (d, *J* = 14.0 Hz, 1 H), 3.31 (d, *J* = 14.0 Hz, 1 H), 1.86 (s, 3 H); minor rotomer: 7.44-7.16 (m, 10 H), 6.57 (s, 1 H), 4.97 (s, 2 H), 3.71 (d, *J* = 12.0 Hz, 1 H), 3.40 (d, *J* = 12.0 Hz, 1 H), 1.74 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 173.5, 173.0, 152.1, 151.2, 136.5, 136.1, 134.9, 134.8, 133.6, 133.3, 132.6, 132.5, 130.0, 129.9, 129.2, 129.1, 128.7, 128.6, 128.3, 128.2, 128.0, 127.6, 126.9, 90.1, 67.9, 67.3,

65.8, 64.2, 63.0, 43.0, 40.1, 24.4, 23.4, 15.3; FAB LRMS *m/z* (M+H) 468, (M − CH_2S-4-ClPh) 310. Anal. Calcd for $C_{25}H_{22}NO_4ClS$: C, 64.16; H, 4.74; N, 2.99; S, 6.85. Found: C, 64.32; H, 4.68; N, 3.16.

(*R*)-2-Benzyloxycarbonylamino-3-chloro-2-methylpropionic acid methyl ester (11a). Compound (**10a**) (0.2000 g, 0.556 mmol) was dissolved in THF (1.7 mL) under N_2, cooled to 0 °C, and a 1 M solution of NaOMe in MeOH (1.11 mL, 1.11 mmol, 2 equiv.) was added dropwise, with stirring. The solution was stirred for 20 min, then quenched by addition of H_2O, and the mixture extracted twice with ether. The combined ether layers were washed with brine, dried over $MgSO_4$, filtered, and solvent removed under vacuum. The product was purified by flash chromatography (4:1 hexane/ether) and was obtained as a clear colorless oil (0.1354 g, 85%): TLC R_f 0.17 (4:1 hexane/ether); $[\alpha]^{25}_D$ = +10.0º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3361, 3033, 2954, 1724, 1510, 1453, 1309, 1277, 1063; ^{1}H NMR ($CDCl_3$, δ ppm) 7.40-7.31 (m, 5 H), 5.81 (br s, 1 H), 5.1 (s, 2 H), 4.24 (br d, *J* = 11.2 Hz, 1 H), 3.96 (d, *J* = 11.2 Hz, 1 H), 3.82 (s, 3 H), 1.64 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 172.1, 154.5, 136.1, 128.5, 128.1, 127.9, 66.6, 60.6, 53.1, 47.1, 21.8; FAB LRMS *m/z* (M+H) 286, (M+H − CO_2) 242; Anal. Calcd for $C_{13}H_{16}NO_4Cl$: C, 54.65; H, 5.64; N, 4.90. Found: C, 54.31; H, 5.82; N, 4.83.

(*R*)-2-Benzyloxycarbonylamino-3-iodo-2-methylpropionic acid methyl ester (11b). Compound (**10b**) (1.3706 g, 3.037 mmol) was dissolved in THF (9 mL) under N_2, cooled to −40 °C, and a 1 M solution of NaOMe in MeOH (6.075 mL, 6.075 mmol, 2 equiv.) was added dropwise, with stirring over 10 min. The solution was stirred for 2 h at −40 °C, then allowed to slowly warm to −20 °C over 1 h. The reaction was quenched by addition of H_2O (66 mL), and the resulting mixture was extracted with ether (4 X 22 mL). The combined ether fractions were washed with brine (22 mL), dried over $MgSO_4$, filtered, and solvent removed under vacuum. The product was purified by flash chromatography (4:1 hexane/ether) and was obtained as a clear colorless oil (0.9726 g, 85%): TLC R_f 0.17 (4:1 hexane/ether); $[\alpha]^{27}_D$ = +13.8º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3366, 2952, 1724, 1504, 1455, 1304, 1276, 1110; ^{1}H NMR ($CDCl_3$, δ ppm) 7.42-7.31 (m, 5 H), 5.83 (br s, 1 H); 5.14 (d, *J* = 14.4 Hz, 1 H); 5.12 (d, *J* = 14.4 Hz, 1 H); 4.08 (br d, *J* = 10.0 Hz, 1 H), 3.82 (s, 3 H), 3.73 (d, *J* = 10.0 Hz, 1 H), 1.61 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 171.6, 154.2, 136.2, 128.5, 128.1, 127.8, 66.6, 59.9, 53.3, 23.1, 12.0; FAB HRMS *m/z* (M+H) calcd 378.0202, found 378.0212. Anal. Calcd for $C_{13}H_{16}NO_4I$: C, 41.40; H, 4.28; N, 3.71. Found: C, 41.29; H, 4.01; N, 3.85.

(*R*)-2-Benzyloxycarbonylamino-2-methyl-3-methylsulfanylpropionic acid methyl ester (11d). Following the procedure used for synthesis of **11a**, the product was obtained as a light yellow oil (89%): TLC R_f 0.15 (4:1 hexane/ether); $[\alpha]^{25}_D$ = +10.6º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3356, 2951, 1722, 1504, 1454, 1308, 1227, 1058; ^{1}H NMR ($CDCl_3$, δ ppm) 7.43-7.29 (m, 5 H), 5.89 (br s, 1 H), 5.11 (d, *J* = 12.0

Hz, 1 H), 5.08 (d, *J* = 12.0 Hz, 1 H), 3.77 (s, 3 H), 3.35 (br d, *J* = 14.0 Hz, 1 H), 3.06 (br d, *J* = 14.0 Hz, 1 H), 2.04 (s, 3 H), 1.70 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 173.5, 154.5, 136.3, 128.4, 128.0, 128.05, 66.4, 60.9, 52.8, 40.4, 23.3, 16.8; FAB LRMS *m/z* (M+H) 298.1; Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71. Found: C, 56.71; H, 6.71; N, 4.87.

(*R*)-2-Benzyloxycarbonylamino-3-(4-chlorophenylsulfanyl)-2-methylpropionic acid methyl ester (11e). Following the procedure used for synthesis of **11a**, the product was obtained as a clear colorless oil (85%): TLC R_f 0.14 (4:1 hexane/ether); $[\alpha]^{25}_D$ = +18.1º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3359, 2952, 1721, 1503, 1308, 1095, 1057; ^{1}H NMR ($CDCl_3$, δ ppm) 7.39-7.21 (m, 9 H), 5.79 (s, 1 H), 4.94 (d, *J* = 12.0 Hz, 1 H), 4.82 (d, *J* = 12.0 Hz, 1 H), 3.86 (d, *J* = 13.6 Hz, 1 H), 3.67 (s, 3 H), 3.43 (d, *J* = 13.6 Hz, 1 H), 1.64 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 173.0, 154.1, 136.0, 133.8, 132.7, 132.6, 128.8, 128.4, 128.1, 128.0, 66.5, 61.0, 52.8, 40.5, 23.4; FAB LRMS *m/z* (M+H) 394; Anal. Calcd for $C_{19}H_{20}NO_4ClS$: C, 57.94; H, 5.12; N, 3.56. Found: C, 58.05; H, 5.24; N, 3.59.

(*S*)-2-Isopropyl-4-methyl-4,5-dihydrooxazole-4-carboxylic acid methyl ester (12). Iodide (**6b**) (0.1402 g, 0.448 mmol) was dissolved in THF (1.5 mL), and DBU (134 μL, 0.896 mmol) was added. The solution was heated at 65 °C for 30 min, then cooled to rt, concentrated, and loaded directly onto a flash column (3:1 hexane/EtOAc). The product was isolated as a clear colorless liquid (49.5 mg, 60%): TLC R_f 0.29 (3:1 hexane/EtOAc); $[\alpha]^{25}_D$ = +51.1º (*c* 0.090, $CHCl_3$); IR (NaCl, cm^{-1}) 2975, 1740, 1658, 1455, 1291, 1213, 1148. ^{1}H NMR ($CDCl_3$, δ ppm) 4.57 (d, *J* = 8.8 Hz, 1 H), 3.94 (d, *J* = 8.8 Hz, 1 H), 3.74 (s, 3 H), 2.59 (heptet, *J* = 6.8 Hz, 1 H), 1.47 (s, 3 H), 1.18 (d, *J* = 6.8 Hz, 3 H), 1.17 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 173.9, 173.0, 75.5, 73.5, 52.5, 28.1, 25.1, 19.5, 19.4; FAB LRMS *m/z* (M+H) 186, (M − CO_2Me) 126; Anal. Calcd for $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.02; H, 8.35; N, 7.69.

(*R*)-2-Methyl-3-methylsulfanyl-2-(2-methylthiopropionylamino)propionic acid methyl ester (13d). TLC R_f 0.42 (3:1 hexane/EtOAc); IR (NaCl, cm^{-1}) 3319, 2970, 1738, 1433, 1285, 1116, 1018; ^{1}H NMR ($CDCl_3$, δ ppm) 7.92 (br s, 1 H), 3.82 (d, *J* = 14.0 Hz, 1 H), 3.79 (s, 3 H), 3.39 (d, *J* = 14.0 Hz, 1 H), 2.84 (heptet, *J* = 6.8 Hz, 1 H), 2.13 (s, 3 H), 1.80 (s, 3 H), 1.27 (d, *J* = 6.8 Hz, 6 H); FAB LRMS *m/z* (M+H) 250.

(*S*)-4-Chloromethyl-2-isopropyl-4-methyl-4*H*-thiazol-5-one (14a). IR (NaCl, cm^{-1}) 2966, 2928, 1720, 1628, 1024; ^{1}H NMR ($CDCl_3$, δ ppm) 3.82 (d, *J* = 10.8 Hz, 1 H), 3.78 (d, *J* = 10.8 Hz, 1 H), 2.98 (heptet, *J* = 6.8 Hz, 1 H), 1.44 (s, 3 H), 1.32 (d, *J* = 6.8 Hz, 3 H), 1.31 (d, *J* = 6.8 Hz, 3 H);

(*S*)-4-Benzylsulfanylmethyl-2-isopropyl-4-methyl-4*H*-thiazol-5-one (14c). TLC R_f 0.47 (6:1 hexane/EtOAc); IR (NaCl, cm^{-1}) 2972, 2929, 1716, 1625, 1454, 1025; ^{1}H NMR ($CDCl_3$, δ ppm) 7.34-

7.23 (m, 5 H), 3.76 (d, *J* = 13.2 Hz, 1 H), 3.71 (d, *J* = 13.2 Hz, 1 H), 2.98 (heptet, *J* = 6.8 Hz, 1 H), 2.90 (d, *J* = 14.0 Hz, 1 H), 2.80 (d, *J* = 14.0 Hz, 1 H), 1.41 (s, 3 H), 1.34 (d, *J* = 6.8 Hz, 1 H), 1.33 (d, *J* = 14.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, δ ppm) 209.8, 172.6, 137.8, 129.0, 128.4, 127.0, 86.8, 38.2, 37.5, 36.3, 23.6, 20.3, 20.2; FAB LRMS *m/z* (M+H) 294.

(*S*)-2-Isopropyl-4-methyl-4-methylsulfanylmethyl-4*H*-thiazol-5-one (14d). The product was isolated as a yellow liquid (83%): TLC R_f 0.44 (6:1 hexane/EtOAc); IR (NaCl, cm^{-1}) 2971, 2926, 1719, 1626; ^{1}H NMR ($CDCl_3$, δ ppm) 3.02 (d, *J* = 14.0 Hz, 1 H), 2.96 (heptet, *J* = 6.8 Hz, 1 H), 2.89 (d, *J* = 14.0 Hz, 1 H), 2.14 (s, 3 H), 1.43 (s, 3 H), 1.32 (d, *J* = 6.8 Hz, 3 H), 1.31 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 209.9, 172.7, 86.8, 42.1, 36.2, 23.5, 20.2, 20.1, 17.9; FAB LRMS *m/z* (M+H) 218; Anal. Calcd for $C_9H_{15}NOS_2$: C, 49.73; H, 6.96; N, 6.44; S, 29.51. Found: C, 49.53; H, 7.32; N, 6.28; S, 29.26.

(*S*)-4-(4-Chlorophenylsulfanylmethyl)-2-isopropyl-4-methyl-4*H*-thiazol-5-one (14e). TLC R_f 0.44 (6:1 hexane/EtOAc); IR (NaCl, cm^{-1}) 2973, 2930, 1713, 1627, 1477, 1095, 1012; ^{1}H NMR ($CDCl_3$, δ ppm) 7.31 (AA'XX' pattern, *J* = 8.4 Hz, 2 H), 7.23 (AA'XX' pattern, *J* = 8.4 Hz, 2 H), 3.49 (d, *J* = 13.2 Hz, 1 H), 3.28 (d, *J* = 13.2 Hz, 1 H), 2.86 (heptet, *J* = 7.2 Hz, 1 H), 1.46 (s, 3 H), 1.22 (d, *J* = 7.2 Hz, 1 H), 1.19 (d, *J* = 7.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, δ ppm) 210.0, 172.0, 135.5, 133.2, 131.1, 128.8, 86.2, 42.0, 36.2, 23.7, 20.0, 19.9; FAB LRMS *m/z* (M+H) 314, (M-CH_2SPhCl) 157.

(*S*)-Thioacetic acid *S*-(2-isopropyl-4-methyl-5-oxo-4,5-dihydrothiazol-4-ylmethyl) ester (14h). TLC R_f 0.33 (6:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$, δ ppm) 3.40 (d, *J* = 13.5 Hz, 1 H), 3.33 (d, *J* = 13.5 Hz, 1 H), 2.91 (heptet, *J* = 6.6 Hz, 1 H), 2.33 (s, 3 H), 1.47 (s, 3 H), 1.28 (d, *J* = 6.6 Hz, 3 H), 1.27 (d, *J* = 6.6 Hz, 3 H); FAB LRMS *m/z* (M+H) 246, (M-Me) 230, (M-Ac) 202.

(*R*)-2-(2-Chloro-1-isobutyrylamino-1-methylethyl)-5-methyloxazole-4-carboxylic acid methyl ester (15a). The protected amine (**20a**) (32.1 mg, 0.0875 mmol) was dissolved in MeOH (0.5 mL), 10% palladium on carbon (16 mg) was added, and the mixture stirred vigorously under a balloon atmosphere of hydrogen. After 1 h, the reaction was filtered through Celite and concentrated to give the amine as a clear colorless oil in quantitative yield. This amine was dissolved in CH_2Cl_2 (0.45 mL), diisopropylethylamine (79.0 μL, 0.451 mmol) and DMAP (11.0 mg, 0.090 mmol) were added under N_2, and the solution cooled to −78 °C. Isobutyryl chloride (28.0 μL, 0.271 mmol) was added dropwise, with stirring. After 3 h the reaction was warmed to rt, concentrated, and loaded directly onto a flash column (1:1 hexane/EtOAc). The product was obtained as a clear colorless oil (22.6 mg, 83%): TLC R_f 0.47 (1:1 hexane/EtOAc); $[\alpha]^{25}_D$ = +2.77º (*c* 2.455, $CHCl_3$); IR (NaCl, cm^{-1}) 3312, 2972, 1728, 1667, 1538, 1443, 1352, 1198, 1094; ^{1}H NMR ($CDCl_3$, δ ppm) 6.49 (br s, 1 H), 4.42 (d, *J* = 11.2 Hz, 1 H), 4.13 (d, *J* = 11.2 Hz, 1 H), 3.90 (s, 3 H), 2.62 (s, 3 H), 2.46 (heptet, *J* = 6.8 Hz, 1 H), 1.79 (s, 3 H), 1.16 (d, *J* = 6.8 Hz, 3

H), 1.15 (d, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 176.9, 162.3, 162.1, 156.9, 127.2, 56.7, 51.9, 47.6, 35.7, 23.1, 19.4, 19.2, 12.1; FAB LRMS *m/z* (M+H) 303.1.

(*R*)-2-(2-Benzylsulfanyl-1-isobutyrylamino-1-methylethyl)-5-methyloxazole-4-carboxylic acid methyl ester (15c). The protected amine (**20c**) (0.4642 g, 1.016 mmol) was dissolved in CH_2Cl_2 (19 mL), sat. HBr in AcOH (9.5 mL) was added, and the solution stirred at rt for 2 h. Volatile components were removed in a stream of N_2 followed by vacuum to yield the crude hydrobromide salt. Water was added giving a milky mixture, which was washed three times with hexane to remove benzyl bromide. The aqueous solution was treated with concentrated NH_4OH until basic (pH ≥ 9), and extracted three times with CH_2Cl_2. The combined CH_2Cl_2 layers were washed with brine, dried over $NaSO_4$, filtered, and solvent removed under vacuum. The pure amine was obtained as a clear colorless oil (0.2962 g, 91%).

This amine was dissolved in CH_2Cl_2 (5.5 mL), triethylamine (709 μL, 5.083 mmol) and DMAP (0.1242 g, 1.016 mmol) were added under N_2, and the solution cooled to −78 °C. Isobutyryl chloride (320 μL, 3.0493 mmol) was added dropwise, with stirring. After 2 h the reaction was warmed to rt and washed successively with 1 N HCl (3 X 2 mL), sat. aq. $NaHCO_3$ (2 X 2 mL), brine (2 mL), and dried over $NaSO_4$. The mixture was filtered, concentrated, and the filtrate purified by flash chromatography (1:1 hexane/EtOAc), giving the product as a clear colorless oil, which slowly gave crystals from EtOAc (0.3486 g, 88%): TLC R_f 0.42 (1:1 hexane/EtOAc); mp 87-88 °C; $[\alpha]^{25}_D$ = +1.7º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3320, 2971, 1725, 1662, 1527, 1442, 1351, 1089; ^{1}H NMR ($CDCl_3$, δ ppm) 7.27-7.12 (m, 5 H), 6.59 (br s, 1 H), 3.80 (s, 3 H), 3.50 (s, 2 H), 3.36 (d, J = 13.6 Hz, 1 H), 3.16 (d, J = 13.6 Hz, 1 H), 2.34 (heptet, J = 6.8 Hz, 1 H), 1.66 (s, 3 H), 1.07 (d, J = 6.8 Hz, 3 H), 1.06 (d, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 176.6, 163.6, 162.4, 156.3, 137.9, 128.6, 128.4, 127.1, 127.0, 55.9, 51.7, 39.3, 37.1, 35.5, 33.5, 24.3, 19.3, 19.2, 11.9; FAB HRMS *m/z* (M+H) calcd 391.1691, found 391.1694. Anal. Calcd for $C_{20}H_{26}N_2O_4S$: C, 61.51; H, 6.71; N, 7.17. Found: C, 61.77; H, 6.77; N, 7.32.

[2-(1-Isobutyrylamino-2-mercapto-1-methylethyl)-5-methyloxazole-4-carboxylic acid methyl ester] disulfide (15f). Following the procedure used for synthesis of **6f**, the product was obtained as a white solid (71%): TLC R_f 0.22 (1:3 hexane/EtOAc); mp 117-119 °C; $[\alpha]^{25}_D$ = +90.0º (*c* 1.00, $CHCl_3$); IR (KBr, cm^{-1}) 3314, 2972, 1719, 1663, 1529, 1443, 1385, 1193, 1088; ^{1}H NMR ($CDCl_3$, δ ppm) 6.67 (br s, 1 H), 3.88 (s, 3 H), 3.72 (d, J = 14.4 Hz, 1 H), 3.38 (d, J = 14.4 Hz, 1 H), 2.59 (s, 3 H), 2.43 (heptet, J = 6.8 Hz, 1 H), 1.73 (s, 3 H), 1.12 (d, J = 6.8 Hz, 6 H); ($CDCl_3$, δ ppm) 176.7, 162.8, 162.4, 156.6, 127.2, 56.1, 51.9, 45.9, 35.7, 24.5, 19.4, 19.2, 12.1; FAB LRMS *m/z* (M+H) 599.4; Anal. Calcd for $C_{26}H_{38}N_4O_8S_2$: C, 52.16; H, 6.40; N, 9.36. Found: C, 51.87; H, 6.61; N, 8.95.

(*R*)-2-[1-Isobutyrylamino-2-(4-methoxybenzylsulfanyl)-1-methylethyl]-5-methyloxazole-4-carboxylic acid methyl ester (15j). Following the procedure used for synthesis of **15c**, but substituting diisopropylethylamine for triethylamine, the product was obtained as a clear colorless oil (80%): TLC R_f 0.37 (1:1 hexane/EtOAc); $[\alpha]^{25}_D$ = +3.2º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3319, 2968, 1722, 1667, 1512, 1441, 1350, 1249, 1089; ^{1}H NMR ($CDCl_3$, δ ppm) 7.21 (AA'XX' pattern, *J* = 8.4 Hz, 2 H), 6.77 (AA'XX' pattern, *J* = 8.4 Hz, 2 H), 6.53 (br s, 1 H), 3.91 (s, 3 H), 3.73 (s, 3 H), 3.49 (s, 2 H), 3.37 (d, *J* = 13.6 Hz, 1 H), 3.15 (d, *J* = 13.6 Hz, 1 H), 2.52 (s, 3 H), 2.35 (heptet, *J* = 6.8 Hz, 1 H), 1.70 (s, 3 H), 1.10 (d, *J* = 6.8 Hz, 3 H), 1.09 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 176.6, 163.6, 162.4, 158.6, 156.3, 129.8, 129.75, 127.1, 113.8, 56.0, 55.1, 51.8, 39.3, 36.6, 35.6, 24.4, 19.4, 19.3, 12.0; FAB LRMS *m/z* (M+H) 421, (PMB+) 121; Anal. Calcd for $C_{21}H_{28}N_2O_5S$: C, 59.98; H, 6.71; N, 6.66. Found: C, 59.80; H, 6.88; N, 6.44.

(*R*)-2-(2-Isopropyl-4-methyl-4,5-dihydrothiazol-4-yl)-5-methyloxazole-4-carboxylic acid methyl ester (16). Following the procedures used for synthesis of **7**, the product (**16**) was obtained as a clear colorless oil: TLC R_f 0.40 (2:1 hexane/EtOAc); $[\alpha]^{25}_D$ = +61.3º (*c* 0.411, $CHCl_3$); IR (NaCl, cm^{-1}) 2969, 1738, 1721, 1619, 1441, 1351, 1191, 1087; ^{1}H NMR ($CDCl_3$, δ ppm) 3.97 (d, *J* = 11.2 Hz, 1 H), 3.91 (s, 3 H), 3.29 (d, *J* = 11.2 Hz, 1 H), 2.86 (heptet, *J* = 6.8 Hz, 1 H), 2.64 (s, 3 H), 1.22 (d, *J* = 6.8 Hz, 6 H); ^{13}C NMR ($CDCl_3$, δ ppm) 178.2, 163.7, 162.7, 157.2, 127.1, 79.0, 51.9, 41.9, 33.9, 24.3, 21.2, 21.1, 12.1; FAB LRMS *m/z* (M+H) 283.

(*R*)-2-Benzyloxycarbonylamino-3-chloro-2-methylpropionic acid (17a). Compound (**10a**) (0.1099 g, 0.3846 mmol) was dissolved in THF (5.7 mL), and H_2O (1.9 mL) was added, followed by LiOH•H_2O (32.3 mg, 0.7693 mmol). The heterogeneous mixture was stirred briskly at rt, and after 6 h the reaction was complete. The THF was evaporated and the remaining water solution acidified to pH≤1 with 2 N HCl. This mixture was extracted twice with ether, and the combined ether layers washed with brine, dried over $MgSO_4$, filtered, and solvent removed under vacuum. The product was obtained as a clear colorless oil (88.0 mg, 84%): TLC R_f 0.20 (75:25:2 hexane/EtOAc/AcOH); $[\alpha]^{25}_D$ = +9.8º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3406, 3334, 3035, 1713, 1515, 1455, 1285, 1065; ^{1}H NMR ($CDCl_3$, δ ppm) 9.29 (br s, 1 H), 7.40-7.34 (m, 5 H), 5.71 (br s, 1 H), 5.13 (s, 2 H), 4.18 (br d, *J* = 11.2 Hz, 1 H), 4.04 (d, *J* = 11.2 Hz, 1 H), 1.69 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 175.8, 154.8, 135.8, 128.5, 128.2, 127.9, 66.9, 60.4, 46.9, 21.8; FAB LRMS *m/z* (M+H) 272; Anal. Calcd for $C_{12}H_{14}NO_4Cl$: C, 53.05; H, 5.19; N, 5.16. Found: C, 52.95; H, 5.30; N, 4.90.

(*R*)-2-Benzyloxycarbonylamino-3-(4-methoxybenzylsulfanyl)-2-methylpropionic acid (17j). Compound (**22**) (3.90 g, 9.66 mmol) was dissolved in THF (144 mL) and H_2O (48 mL) was added, followed by LiOH•H_2O (0.811 g, 19.3 mmol), with stirring. After stirring for 20 h, the reaction mixture

was concentrated under vacuum to remove THF, and the remaining aqueous solution acidified to pH≤1 with 2 N HCl. This mixture was extracted with ether (3 X 48 mL), and the combined ether fractions were washed with brine, dried over $MgSO_4$, filtered, and the solvent removed under vacuum. The product was obtained as a viscous, clear, colorless oil (3.63 g, 97%): TLC R_f 0.26 (75:25:2 hexane/EtOAc/AcOH); $[\alpha]^{25}_D = -1.5°$ (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3400, 2979, 1730, 1609, 1513, 1451, 1238; ^1H NMR ($CDCl_3$, δ ppm) 9.55 (br s, 1 H), 7.36-7.27 (m, 5 H), 7.19 (AA'XX' pattern, *J* = 8.4 Hz, 2 H), 6.83 (AA'XX' pattern, *J* = 8.4 Hz, 2 H), 5.95 (br s, 1 H), 5.13 (s, 2 H), 3.78 (s, 3 H), 3.65 (d, *J* = 13.2 Hz, 1 H), 3.61 (d, *J* = 13.2 Hz, 1 H), 3.29 (br d, *J* = 13.2 Hz, 1 H), 3.08 (d, *J* = 13.2 Hz, 1 H), 1.64 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 177.1, 158.6, 154.8, 136.1, 129.9, 129.85, 128.5, 128.1, 128.0, 113.9, 67.8, 60.3, 55.2, 36.7, 25.5, 23.3; FAB HRMS *m/z* (M+^{7}Li) calcd 396.1457, found 396.1446. Anal. Calcd for $C_{20}H_{23}NO_5S$: C, 61.68; H, 5.95; N, 3.60; S, 8.23. Found: C, 61.32; H, 6.33; N, 3.68; S, 8.08.

(*R*)-*N*-Benzyloxycarbonyl-2-chloromethylalanine-L-threonine methyl ester (18a). Compound (**17a**) (2.881 g, 10.603 mmol), threonine methyl ester hydrochloride salt (2.431 g, 14.334 mmol), CH_2Cl_2 (13.8 mL), diisopropylethylamine (6.90 mL, 39.80 mmol), and DMAP (1.363 mmol, 11.140 mmol) were mixed. The resulting solution was cooled to 0 °C and PyBroP (6.188 g, 13.309 mmol) was added, with stirring. The reaction solution was warmed to rt and stirred for 24 h. The solution was diluted with CH_2Cl_2, washed three times with 10% aqueous $KHSO_4$, dried over $MgSO_4$, and filtered. The filtrate was concentrated and purified by flash chromatography (1:1 hexane/EtOAc) and the product obtained as an oil that crystallized (3.627 g, 88%): TLC R_f 0.27 (1:1 hexane/EtOAc); mp 109-111 °C; $[\alpha]^{25}_D = -19.0°$ (*c* 1.00, $CHCl_3$); IR (KBr, cm^{-1}) 3454, 3300, 2987, 1749, 1642, 1519, 1263, 1205; ^1H NMR ($CDCl_3$, δ ppm) 7.38-7.33 (m, 5 H), 6.97 (br d, *J* = 9.2 Hz, 1 H), 5.37 (br s, 1 H), 5.17 (d, *J* = 12.4 Hz, 1 H), 5.09 (d, *J* = 12.4 Hz, 1 H), 4.55 (dd, *J* = 9.2, 2.8 Hz, 1 H), 4.33 (d, *J* = 11.6 Hz, 1 H), 4.21 (m, 1 H), 3.96 (d, *J* = 11.6 Hz, 1 H), 3.76 (s, 3 H), 1.69 (br s, 1 H), 1.57 (s, 3 H), 1.17 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 171.8, 171.0, 155.0, 135.5, 128.5, 128.3, 128.1, 68.4, 67.3, 60.1, 57.1, 52.5, 47.3, 22.9, 19.0; FAB LRMS *m/z* (M+H) 387; Anal. Calcd for $C_{17}H_{23}N_2O_6Cl$: C, 52.78; H, 5.99; N, 7.24. Found: C, 53.00; H, 5.92; N, 7.03.

(*R*)-*N*-Benzyloxycarbonyl-*S*-benzyl-2-methylcysteine-L-threonine methyl ester (18c). Following the procedure used for synthesis of **18a**, the product was obtained as a viscous oil that slowly crystallized upon standing (90%): TLC R_f 0.24 (1:1 hexane/EtOAc); mp 79-80 °C; $[\alpha]^{25}_D = -2.96°$ (*c* 0.135, $CHCl_3$); IR (KBr, cm^{-1}) 3516, 3426, 3260, 1738, 1722, 1657, 1530, 1511; ^1H NMR ($CDCl_3$, δ ppm) 7.36-7.22 (m, 10 H), 6.95 (d, *J* = 8.8 Hz, 1 H), 5.46 (s, 1 H), 5.10 (d, *J* = 12.4 Hz, 1 H), 5.06 (d, *J* = 12.4 Hz, 1 H), 4.53 (dd, *J* = 8.8, 2.8 Hz, 1 H), 4.21 (dq, *J* = 6.4, 6.4, 6.4, 2.8 Hz, 1 H), 3.74 (s, 3 H), 3.69 (d, *J* = 13.2 Hz, 1 H), 3.65 (d, *J* = 13.2 Hz, 1 H), 3.33 (d, *J* = 13.6 Hz, 1 H), 3.02 (d, *J* = 13.6 Hz, 1 H), 1.87 (br s, 1 H), 1.51

(s, 3 H), 1.17 (d, J = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 173.3, 171.2, 171.15, 155.0, 138.0, 135.9, 128.8, 128.5, 128.2, 128.1, 127.1, 68.2, 67.0, 60.0, 57.4, 52.4, 38.1, 37.7, 23.6, 19.9; FAB HRMS *m/z* (M+H) calcd 475.1903, found 475.1896. Anal. Calcd for $C_{24}H_{30}N_2O_6S$: C, 60.74; H, 6.37; N, 5.90; S, 6.76. Found: C, 60.56; H, 6.32; N, 5.84; S, 6.89.

(*R*)-*N*-Benzyloxycarbonyl-*S*-4-methoxybenzyl-2-methylcysteine-L-threonine methyl ester (18j). Following the procedure used for synthesis of **18a**, the product was obtained as a viscous oil that slowly crystallized upon standing (92%): TLC R_f 0.14 (50:1 CH_2Cl_2/MeOH); $[\alpha]^{27}_D$ = +19.2º (*c* 1.00, $CHCl_3$); mp 88-90 °C; IR (KBr, cm^{-1}) 3375, 2952, 1730, 1663, 1513, 1252; ^{1}H NMR ($CDCl_3$, δ ppm) 7.34-7.27 (m, 5 H), 7.17 (AA'XX', J = 8.8 Hz, 2 H), 7.05 (d, J = 8.8 Hz, 1 H), 6.81 (AA'XX', J = 8.8 Hz, 2 H), 5.72 (br s, 1 H), 5.10 (d, J = 12.4 Hz, 1 H), 5.06 (d, J = 12.4 Hz, 1 H), 4.53 (dd, J = 8.8, 2.8 Hz, 1 H), 4.23 (br s, 1 H), 3.76 (s, 3 H), 3.71 (s, 3 H), 3.64 (d, J = 13.2 Hz, 1 H), 3.60 (d, J = 13.2 Hz, 1 H), 3.32 (d, J = 13.6 Hz, 1 H), 3.02 (d, J = 13.6 Hz, 1 H), 2.68 (br s, 1 H), 1.51 (s, 3 H), 1.16 (d, J = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 173.4, 171.2, 158.6, 155.0, 136.0, 129.9, 128.5, 128.2, 128.1, 113.9, 68.2, 67.0, 60.0, 57.4, 55.2, 52.5, 37.9, 37.1, 23.6, 22.4, 19.9; FAB HRMS *m/z* (M+H) calcd 505.2008, found 505.2017. Anal. Calcd for $C_{25}H_{32}N_2O_7S$: C, 59.51; H, 6.39; N, 5.55; S, 6.35. Found: C, 59.48; H, 6.35; N, 5.64; S, 6.48.

(*R*)-2-(2-Benzyloxycarbonylamino-3-chloro-2-methylpropionylamino)-3-oxobutyric acid methyl ester (19a). Alcohol (**18a**) (3.627 g, 9.377 mmol) was dissolved in DMSO (160 mL), and acetic anhydride (20 mL) was added dropwise, with stirring. After careful monitoring by TLC, the reaction was determined to be complete after 4 h. The reaction solution was poured into sat. aq. $NaHCO_3$ (475 mL) and stirred until bubbling had subsided. The mixture was extracted with CH_2Cl_2 (3 X 200 mL), and the combined CH_2Cl_2 layers washed with H_2O (200 mL), brine (200 mL), and dried over Na_2SO_4. The drying agent was filtered, and the filtrate concentrated and purified by flash chromatography (2.5:1 hexane/EtOAc). The product was obtained as 1.4:1 mixture of epimers at C-2, which were inseparable. The mixture was a clear colorless oil that solidified upon standing (2.525 g, 70%): TLC R_f 0.21 (2:1 hexane/EtOAc); IR (NaCl, cm^{-1}) 3326, 2956, 1726, 1671, 1507, 1262, 1203, 1053; ^{1}H NMR ($CDCl_3$, δ ppm) 7.48-7.32 (m, 6 H), 5.53-5.10 (m, 4 H), 4.26 (d, J = 11.6 Hz, 1 H in major epimer), 4.19 (d, J = 11.6 Hz, 1 H in minor epimer), 3.91 (d, J = 11.6 Hz, 1 H in major epimer), 3.89 (d, J = 11.6 Hz, 1 H in minor epimer), 3.81 (s, 3 H in major epimer), 3.80 (s, 3 H in minor epimer), 2.38 (s, 3 H in minor epimer), 2.35 (s, 3 H in major epimer), 1.61 (s, 3 H in minor epimer), 1.58 (s, 3 H in major epimer); ^{13}C NMR ($CDCl_3$, δ ppm) 209.7, 198.0, 197.7, 171.6, 171.4, 166.2, 166.0, 154.8, 135.8, 135.7, 128.5, 128.2, 128.0, 127.9, 67.15, 67.1, 63.0, 62.9, 60.0, 59.9, 53.3, 53.2, 47.8, 47.6, 27.9, 27.6, 22.5, 22.2; FAB LRMS *m/z* (M+H) 385; Anal. Calcd for $C_{17}H_{21}N_2O_6Cl$: C, 53.06; H, 5.50; N, 7.28. Found: C, 53.04; H, 5.56; N, 7.14.

(*R*)-2-(3-Benzylsulfanyl-2-isobutyrylamino-2-methylpropionylamino)-3-oxobutyric acid methyl ester (19c). Following the procedure described for synthesis of **19a**, the product was obtained as a 1:1 mixture of epimers at C-2, which were inseparable. The mixture was a clear colorless oil that solidified upon standing (73%): TLC R_f 0.19 (2:1 hexane/EtOAc); IR (KBr, cm^{-1}) 3247, 3033, 2945, 1754, 1721, 1658, 1537, 1507, 1264, 1053; ^{1}H NMR ($CDCl_3$, δ ppm) 7.45 (br s, 1 H), 7.35-7.12 (m, 10 H), 5.60 (d, 8.8 Hz, 1 H), 5.16 (br s, 1 H), 5.10 (d, *J* = 12.4 Hz, 1 H), 5.06 (d, *J* = 12.4 Hz, 1 H), 3.78 (s, 3 H), 3.67 (s, 2 H), 3.26 (d, *J* = 13.6 Hz, 1 H in one epimer), 3.17 (d, *J* = 13.6 Hz, 1 H in one epimer), 2.98 (d, *J* = 13.6 Hz, 1 H in one epimer), 2.97 (d, *J* = 13.6 Hz, 1 H in one epimer), 2.33 (s, 3 H), 1.55 (s, 3 H in one epimer), 1.53 (s, 3 H in one epimer); ^{13}C NMR ($CDCl_3$, δ ppm) 198.1, 172.8, 172.7, 166.3, 166.2, 154.8, 137.9, 137.8, 136.0, 128.8, 128.6, 128.5, 128.4, 128.1, 128.0, 127.2, 127.1, 66.9, 66.8, 63.0, 59.7, 53.2, 38.8, 38.3, 37.6, 37.5, 27.8, 23.3, 23.0; FAB HRMS *m/z* (M+H) calcd 473.1746, found 473.1736. Anal. Calcd for $C_{24}H_{28}N_2O_6S$: C, 61.00; H, 5.97; N, 5.93; S, 6.78. Found: C, 60.73; H, 6.02; N, 5.87; S, 6.82.

(*R*)-2-[2-Isobutyrylamino-3-(4-methoxybenzylsulfanyl)-2-methylpropionylamino]-3-oxobutyric acid methyl ester (19j). Following the procedure described for synthesis of **19a**, the product was obtained as a white solid (72%): TLC R_f 0.13 (2:1 hexane/EtOAc); $[\alpha]^{25}_D$ = −26.3º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3400, 3234, 1755, 1721, 1667, 1506, 1240; ^{1}H NMR ($CDCl_3$, δ ppm) 7.47 (d, *J* = 6.0 Hz, 1 H), 7.34-7.20 (m, 5 H), 7.18 (AA'XX' pattern, *J* = 8.4 Hz, 2 H), 6.82 (AA'XX' pattern, *J* = 8.4 Hz, 2 H), 5.65 (br s, 1 H), 5.17 (d, *J* = 5.2 Hz, 1 H), 5.10 (d, *J* = 12.4 Hz,1 H), 5.06 (d, *J* = 12.4 Hz,1 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.61 (s, 2 H), 3.24 (d, *J* = 14.0 Hz, 1 H), 2.97 (d, *J* = 14.0 Hz, 1 H), 2.33 (s, 3 H), 1.55 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 198.1, 172.8, 166.3, 158.7, 154.8, 136.0, 129.9, 129.8, 128.4, 128.1, 128.0, 113.9, 66.8, 63.1, 59.7, 55.1, 53.2, 38.2, 37.0, 27.7, 23.3; FAB HRMS *m/z* (M+H) calcd 503.1852, found 503.1845. Anal. Calcd for $C_{25}H_{30}N_2O_7S$: C, 59.75; H, 6.02; N, 5.57; S, 6.38. Found: C, 59.40; H, 6.23; N, 5.55; S, 6.65.

(*R*)-2-(1-Benzyloxycarbonylamino-2-chloro-1-methylethyl)-5-methyloxazole-4-carboxylic acid methyl ester (20a). Triphenylphosphine (3.297 g, 12.571 mmol) was dissolved in CH_2Cl_2 (52 mL), and iodine (3.188 g, 12.571 mmol) was added with stirring. After one minute a homogeneous solution formed, and after 2 min Et_3N (3.50 mL, 25.14 mmol) was added, with stirring. A solution of the β-keto ester (**19a**) (2.419 g, 6.286 mmol) in CH_2Cl_2 (52 mL) was added dropwise over 2 min, with stirring. After 20 min, the reaction solution was washed with a mixture of sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_3$, dried over Na_2SO_4, filtered, and concentrated to a dark red oil. Purification by flash chromatography (3:1 hexane/EtOAc) gave the product as a clear colorless oil (1.588 g, 69%): TLC R_f 0.22 (3:1 hexane/EtOAc); $[\alpha]^{25}_D$ = −9.6º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3342, 2953, 1722, 1622, 1515, 1412, 1258, 1086; ^{1}H NMR ($CDCl_3$, δ ppm) 7.33-7.27 (m, 5 H), 5.93 (br s, 1 H), 5.06 (s, 2 H), 4.24 (br d, *J* = 11.6 Hz, 1 H),

4.14 (d, J = 11.6 Hz, 1 H), 3.89 (s, 3 H), 2.60 (s, 3 H), 1.77 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 162.3, 161.7, 156.9, 154.3, 136.0, 128.4, 128.1, 127.9, 127.3, 66.7, 56.5, 52.0, 48.2, 23.3, 12.0; FAB LRMS *m/z* (M+H) 367.

(*R*)-2-(1-Benzyloxycarbonylamino-2-benzylsulfanyl-1-methylethyl)-5-methyloxazole-4-carboxylic acid methyl ester (20c). Following the procedure described for synthesis of **20a**, the product was obtained as a clear colorless oil (92%): TLC R_f 0.34 (2:1 hexane/EtOAc); $[\alpha]^{25}_D = -0.3°$ (*c* 1.055, $CHCl_3$); IR (NaCl, cm^{-1}) 3344, 2951, 1725, 1712, 1621, 1512, 1245, 1082; ^{1}H NMR ($CDCl_3$, δ ppm) 7.66-7.21 (m, 10 H), 5.93 (br s, 1 H), 5.13 (d, J = 12.6 Hz, 1 H), 5.08 (d, J = 12.6 Hz, 1 H), 3.90 (s, 3 H), 3.62 (s, 2 H), 3.32 (br d, J = 13.6 Hz, 1 H), 3.20 (d, J = 13.6 Hz, 1 H), 2.57 (s, 3 H), 1.75 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 163.3, 162.5, 156.5, 154.5, 137.7, 136.2, 128.8, 128.45, 128.4, 128.1, 128.0, 127.3, 127.1, 66.6, 56.2, 51.9, 39.9, 37.3, 24.7, 12.0; HRMS *m/z* (M+H) calcd 455.1641, found 455.1631. Anal. Calcd for $C_{24}H_{26}N_2O_5S$: C, 63.42; H, 5.77; N, 6.16; S, 7.05. Found: C, 63.11; H, 5.84; N, 6.10; S, 6.82.

(*R*)-2-[1-Benzyloxycarbonylamino-2-(4-methoxybenzylsulfanyl)-1-methylethyl]-5-methyloxazole-4-carboxylic acid methyl ester (20j). Following the procedure described for synthesis of **20a**, the product was obtained as a clear colorless oil (90%): TLC R_f 0.24 (2:1 hexane/EtOAc); $[\alpha]^{25}_D = +0.9°$ (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}, KBr) 3343, 2952, 1721, 1512, 1250; ^{1}H NMR ($CDCl_3$, δ ppm) 7.28-7.23 (m, 5 H), 7.10 (AA'XX' pattern, J = 8.4 Hz, 2 H), 6.77 (AA'XX' pattern, J = 8.4 Hz, 2 H), 6.00 (br s, 1 H), 5.02 (s, 2 H), 3.89 (s, 3 H), 3.71 (s, 3 H), 3.48 (s, 2 H), 3.25-3.16 (m, 2 H), 2.56 (s, 3 H), 1.71 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 163.4, 162.4, 158.6, 156.4, 154.5, 136.2, 129.9, 129.7, 128.4, 128.0, 127.9, 127.2, 113.8, 66.5, 56.1, 55.1, 51.8, 39.7, 36.7, 24.6, 12.0; HRMS *m/z* (M+H) calcd 485.1746, found 485.1739. Anal. Calcd for $C_{25}H_{28}N_2O_6S$: C, 61.97; H, 5.82; N, 5.78. Found: C, 61.80; H, 5.81; N, 5.87.

(*S*)-1-Benzyloxycarbonyl-2-methylaziridine-2-carboxylic acid methyl ester (21). Compound (**11b**) (15.244 g, 40.41 mmol) was dissolved in MeCN (2 L) and Ag_2O (26.16 g, 112.9 mmol) added. The mixture was heated at reflux with stirring for 30 min, then cooled to rt. The mixture was vacuum filtered through Celite and the filterate concentrated under vacuum to a liquid-solid residue. This residue was extracted with ether (475 mL), vacuum filtered through Celite, and concentrated to a clear colorless liquid (10.025 g, 100%): TLC R_f 0.13 (4:1 hexane/ether); $[\alpha]^{27}_D = +28.0°$ (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 2955, 1740, 1727, 1240; ^{1}H NMR ($CDCl_3$, δ ppm) 7.41-7.31 (m, 5 H), 5.17 (d, J = 12.0 Hz, 1 H), 5.13 (d, J = 12.0 Hz, 1 H), 3.61 (s, 3 H), 2.81 (d, J = 1.2 Hz, 1 H), 2.26 (d, J = 1.2 Hz, 1 H), 1.52 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 169.8, 160.2, 135.5, 128.4, 128.3, 128.0, 68.2, 52.6, 41.3, 37.8, 17.6; FAB HRMS *m/z* (M+H) calcd 250.1079, found 250.1085. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.42; H, 6.04; N, 5.43.

(*R*)-2-Benzyloxycarbonylamino-3-(4-methoxybenzylsulfanyl)-2-methylpropionic acid methyl ester (11j) and (*S*)-3-Benzyloxycarbonylamino-2-(4-methoxybenzylsulfanyl)-2-methylpropionic acid methyl ester (22). Aziridine (**21**) (0.4979 g, 2.000 mmol) was dissolved in CH_2Cl_2 (1 mL), and PMBSH (1 mL) was added followed by BF_3•OEt_2 (25.3 μL, 0.200 mmol, 0.1 equiv.), with stirring. After 24 h CH_2Cl_2 was evaporated, and the reaction mixture loaded directly onto a flash column (4:1 → 3:1 hexane/ether). The products were obtained as clear colorless oils.

11j: (0.3712 g, 46%): TLC R_f 0.18 (2:1 hexane/ether); $[\alpha]^{27}_D$ = +10.8º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3350, 2952, 1741, 1721, 1513, 1250; ^{1}H NMR ($CDCl_3$, δ ppm) 7.38-7.29 (m, 5 H), 7.18 (AA'XX'pattern, *J* = 8.4 Hz, 2 H), 6.84 (AA'XX' pattern, *J* = 8.4 Hz, 2 H), 5.89 (br s, 1 H), 5.13 (d, *J* = 12.4 Hz, 1 H), 5.09 (d, *J* = 12.4 Hz, 1 H), 3.79 (s, 3 H), 3.75 (br s, 3 H), 3.62 (d, *J* = 13.2 Hz, 1 H), 3.58 (d, *J* = 13.2 Hz, 1 H), 3.29 (br d, *J* = 12.8 Hz, 1 H), 3.02 (br d, *J* = 12.8 Hz, 1 H), 1.60 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 173.4, 158.6, 154.5, 136.3, 130.0, 129.9, 128.4, 128.1, 128.0; FAB HRMS *m/z* (M+^{7}Li) calcd 410.1614, found 410.1616. Anal. Calcd for $C_{21}H_{25}NO_5S$: C, 62.51; H, 6.25; N, 3.47; S, 7.95. Found: C, 62.14; H, 6.57; N, 3.39; S, 7.96.

22: (0.1252 g, 16%): TLC R_f 0.14 (2:1 hexane/ether); $[\alpha]^{27}_D$ = +30.0º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3365, 2952, 1729, 1715, 1513, 1250; ^{1}H NMR ($CDCl_3$, δ ppm) 7.41-7.33 (m, 5 H), 7.22 (AA'XX'pattern, *J* = 8.4 Hz, 2 H), 6.84 (AA'XX' pattern, *J* = 8.4 Hz, 2 H), 5.21 (br t, *J* = 7.6 Hz, 1 H), 5.11 (s, 2 H), 3.79 (s, 3 H), 3.73 (s, 3 H), 3.63 (t, *J* = 7.6 Hz, 2 H), 1.45 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 173.0, 158.7, 156.5, 136.3, 130.0, 128.6, 128.5, 128.1, 128.0, 113.9, 66.8, 55.2, 52.5, 52.0, 46.4, 33.5, 20.8; FAB HRMS *m/z* (M+H) calcd 404.1532, found 404.1527. Anal. Calcd for $C_{21}H_{25}NO_5S$: C, 62.51; H, 6.25; N, 3.47; S, 7.95. Found: C, 62.72; H, 6.50; N, 3.67; S, 7.93.

(*R*)-2-[2-Benzylsulfanyl-1-methyl-1-(2-methylthiopropionylamino)ethyl]-5-methyloxazole-4-carboxylic acid methyl ester (23c). The product was obtained as a white solid (92%): TLC R_f 0.18 (3:1 hexane/EtOAc); mp 115.5-116.5 °C; $[\alpha]^{25}_D$ = −5.3º (*c* 0.68, $CHCl_3$); IR (NaCl, cm^{-1}) 3298, 2968, 1721, 1441, 1351, 1192; ^{1}H NMR ($CDCl_3$, δ ppm) 7.94 (br s, 1 H), 7.33-7.24 (m, 5 H), 3.90 (s, 3 H), 3.71-3.64 (m, 3 H), 3.50 (d, *J* = 13.6 Hz, 1 H), 2.80 (heptet, *J* = 6.8 Hz, 1 H), 1.26 (d, *J* = 6.8 Hz, 3 H), 1.25 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 211.4, 162.7, 162.5, 156.4, 137.8, 128.7, 128.5, 127.2, 127.1, 59.2, 51.9, 45.5, 38.3, 37.3, 23.2, 22.6, 22.5, 12.0; FAB LRMS *m/z* (M+H) 407, (M−Bn) 315; Anal. Calcd for $C_{20}H_{26}N_2O_3S_2$: C, 59.08; H, 6.45; N, 6.89. Found: C, 59.13; H, 6.72; N, 6.72.

(*R,R*)-2-[2-Benzylsulfanyl-1-(3-benzylsulfanyl-2-isobutyrylamino-2-methylpropionylamino)-1-methylethyl]-5-methyloxazole-4-carboxylic acid methyl ester (24c). Following the procedure used for synthesis of **15c**, but substituting diisopropylethylamine for triethylamine, the product was obtained as a

clear colorless oil (19%): TLC R_f 0.24 (3:2 hexane/EtOAc); $[\alpha]^{25}_D$ = −15.5º (*c* 1.12, $CHCl_3$); IR (NaCl, cm^{-1}) 3377, 2970, 1722, 1683, 1495, 1454, 1195, 1099; ^{1}H NMR ($CDCl_3$, δ ppm) 7.65 (br s, 1 H), 7.35-7.21 (m, 10 H), 6.28 (br s, 1 H), 3.87 (s, 3 H), 3,72 (s, 2 H), 3.60 (s, 2 H), 3.66 (d, *J* = 13.2 Hz, 1 H), 3.30 (d, *J* = 13.2 Hz, 1 H), 3.19 (d, *J* = 13.2 Hz, 1 H), 3.00 (d, *J* = 13.2 Hz, 1 H), 2.55 (s, 3 H), 2.32 (heptet, *J* = 6.8 Hz, 1 H), 1.73 (s, 3 H), 1.58 (s, 3 H), 1.16 (d, *J* = 6.8 Hz, 3 H), 1.15 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 177.2, 172.4, 163.2, 162.5, 156.5, 138.1, 137.8, 128.8, 128.75, 128.6, 128.4, 127.2, 127.15, 127.1, 60.1, 56.1, 51.8, 39.7, 38.6, 37.7, 37.2, 36.0, 23.8, 22.8, 19.5, 19.4, 12.0; FAB LRMS *m/z* (M+H) 598.3.

(*R*,*R*)-2-[1-[2-Isobutyrylamino-3-(4-methoxybenzylsulfanyl)-2-methylpropionylamino]-2-(4-methoxybenzylsulfanyl)-1-methylethyl]-5-methyloxazole-4-carboxylic acid methyl ester (24j). Following the procedure used for synthesis of **15c**, but substituting diisopropylethylamine for triethylamine, the product was obtained as a clear colorless oil (44%): TLC R_f 0.26 (1:1 hexane/EtOAc); $[\alpha]^{25}_D$ = −11.8º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3375, 2965, 1721, 1682, 1609, 1513, 1249; ^{1}H NMR ($CDCl_3$, δ ppm) 7.64 (br s, 1 H), 7.22 (AA'XX' pattern, *J* = 8.4 Hz, 2 H), 7.16 (AA'XX' pattern, *J* = 8.4 Hz, 2 H), 6.83 (AA'XX' pattern, *J* = 8.4 Hz, 4 H), 6.29 (br s, 1 H), 3.87 (s, 3 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.67 (s, 2 H), 3.56 (s, 2 H), 3.00 (d, *J* = 13.6 Hz, 1 H), 3.28 (d, *J* = 13.6 Hz, 1 H), 3.17 (d, *J* = 13.6 Hz, 1 H), 2.98 (d, *J* = 13.6 Hz, 1 H), 2.55 (s, 3 H), 2.32 (heptet, *J* = 6.8 Hz, 1 H), 1.73 (s, 3 H), 1.58 (s, 3 H), 1.16 (d, *J* = 6.8 Hz, 3 H), 1.15 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 177.2, 172.5, 163.3, 162.6, 158.8, 158.7, 156.5, 130.2, 130.0, 129.9, 129.8, 127.3, 114.0, 113.9, 60.3, 56.3, 55.3, 51.8, 39.8, 38.7, 37.2, 36.8, 36.1, 23.9, 23.0, 19.6, 19.5, 12.1; HRMS *m/z* (M+H) calcd 658.2621, found 658.2629.

(*R*)-2-(1-Amino-2-benzylsulfanyl-1-methylethyl)-5-methyloxazole-4-carboxylic acid methyl ester (26c). Compound (**20c**) (2.460 g, 5.41 mmol) was dissolved in CH_2Cl_2 (90 mL), cooled to 0 °C, and a saturated solution of HBr in AcOH (45 mL) was added, with stirring. The reaction vessel was fitted with a drying tube and warmed to rt. After 2 h volatile components were removed with a stream of N_2, followed by vacuum drying to give the hydrobromide salt as an orange oil. Water was added (90 mL), and the resulting milky white mixture washed with hexane (3 X 15 mL) to remove benzyl bromide. The aqueous solution was treated with concentrated ammonium hydroxide until basic (pH ≥ 9), and extracted with CH_2Cl_2 (3 X 50 mL). The combined extracts were washed with brine, dried over Na_2SO_4, filtered, and solvent removed under vacuum to give the product as a clear colorless oil (1.642 g, 95%): TLC R_f 0.14 (1:2 hexane/EtOAc); $[\alpha]^{25}_D$ = +15.7º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 2953, 1722, 1620, 1441, 1350, 1205, 1085; ^{1}H NMR ($CDCl_3$, δ ppm) 7.27-7.17 (m, 5 H), 3.86 (s, 3 H), 3.57 (d, *J* = 13.6 Hz, 1 H), 3.53 (d, *J* = 13.6 Hz, 1 H), 2.99 (d, *J* = 13.6 Hz, 1 H), 2.76 (d, *J* = 13.6 Hz, 1 H), 2.56 (s, 3 H), 2.11 (s, 2 H), 1.48 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 166.8, 162.6, 156.4, 137.9, 128.7, 128.4, 127.1, 127.0, 54.3,

51.8, 43.5, 37.4, 27.1, 12.0; FAB LRMS *m/z* (M+H) 321.2, (M−CH_2SBn) 183.1; Anal. Calcd for $C_{16}H_{20}N_2O_3S$: C, 59.98; H, 6.29; N, 8.74. Found: C, 60.11; H, 6.33; N, 8.77.

(*R*)-2-[1-Amino-2-(4-methoxybenzylsulfanyl)-1-methylethyl]-5-methyloxazole-4-carboxylic acid methyl ester (26j). Following the procedure described for synthesis of **26c**, the product (**26j**) was obtained as a clear colorless oil (96%): TLC R_f 0.59 (10:1 EtOAc/Et_3N); $[\alpha]^{27}_D$ = +16.5º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3369, 2952, 1731, 1620, 1513, 1442, 1350, 1249; ^{1}H NMR ($CDCl_3$, δ ppm) 7.17 (AA'XX' pattern, *J* = 8.4 Hz, 2 H), 6.82 (AA'XX' pattern, *J* = 8.4 Hz, 2 H), 3.90 (s, 3 H), 3.78 (s, 3 H), 3.56 (d, *J* = 13.2 Hz, 1 H), 3.52 (d, *J* = 13.2 Hz, 1 H), 3.01 (d, *J* = 13.6 Hz, 1 H), 2.78 (d, *J* = 13.6 Hz, 1 H), 2.60 (s, 3 H), 2.06 (br s, 2 H), 1.52 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 166.8, 162.5, 158.5, 156.3, 129.8, 129.7, 127.1, 113.7, 55.1, 54.23, 51.8, 43.3, 36.8, 27.1, 11.9; FAB HRMS *m/z* (M+H) calcd 351.1379, found 351.1378. Anal. Calcd for $C_{17}H_{22}N_2O_4S$: C, 58.27; H, 6.33; N, 7.99; S, 9.15. Found: C, 58.32; H, 6.56; N, 7.95; S, 9.21.

(*R,R*)-2-[1-(2-Benzyloxycarbonylamino-3-benzylsulfanyl-2-methylpropionylamino)-2-benzyl sulfanyl-1-methylethyl]-5-methyloxazole-4-carboxylic acid methyl ester (27c). The amine (**26c**) (0.3269 g, 1.020 mmol) and the acid (**17c**) (0.4401 g, 1.224 mmol), were mixed and dissolved in CH_2Cl_2 (1.5 mL), along with diisopropylethylamine (533 μL, 3.061 mmol) and DMAP (0.1246 g, 1.020 mmol). The solution was cooled to 0 °C and PyBroP (0.5707 g, 1.224 mmol) was added, with stirring. The solution was warmed to rt and stirred 36 h. It was then concentrated and loaded directly onto a flash column (2:1 hexane/EtOAc). The product was obtained as a viscous, clear, colorless oil (0.4736 g, 70%): TLC R_f 0.25 (2:1 hexane/EtOAc); $[\alpha]^{25}_D$ = −8.39º (*c* 0.465, $CHCl_3$); IR (NaCl, cm^{-1}, CCl_4) 3381, 2936, 1719, 1492, 1453, 1240, 1194, 1088; ^{1}H NMR ($CDCl_3$, δ ppm) 7.37-7.19 (m, 16 H), 5.65 (br s, 1 H), 5.12 (d, *J* = 12.4 Hz, 1 H), 5.09 (d, *J* = 12.4 Hz, 1 H), 3.86 (s, 3 H), 3.68 (s, 2 H), 3.63 (s, 2 H), 3.26 (d, *J* = 13.6 Hz, 1 H), 3.23 (d, *J* = 13.6 Hz, 1 H), 3.17 (d, *J* = 13.6 Hz, 1 H), 2.97 (d, *J* = 13.6 Hz, 1 H), 2.55 (s, 3 H), 1.72 (s, 3 H), 1.54 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 172.3, 163.1, 162.5, 156.4, 154.8, 137.9, 137.8, 136.1, 128.8, 128.7, 128.5, 128.45, 128.4, 128.1, 128.0, 127.3, 127.15, 127.1, 66.7, 60.0, 55.9, 51.8, 40.0, 38.5, 37.6, 37.3, 23.7, 23.2, 12.0; FAB LRMS *m/z* (M+H) 662.3; Anal. Calcd for $C_{35}H_{39}N_3O_6S_2$: C, 63.52; H, 5.94; N, 6.35. Found: C, 63.63; H, 6.09; N, 6.29.

(*R,R*)-2-[1-[2-Isobutyrylamino-3-(4-methoxybenzylsulfanyl)-2-methylpropionylamino]-2-(4-methoxybenzylsulfanyl)-1-methylethyl]-5-methyloxazole-4-carboxylic acid methyl ester (27j). Following the procedure described for synthesis of **27c**, the product (**27j**) was obtained as a clear colorless oil (56%): TLC R_f 0.30 (3:2 hexane/EtOAc); $[\alpha]^{24}_D$ = −5.1º (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3369, 2952, 1723, 1682, 1609, 1513, 1442, 1249; ^{1}H NMR ($CDCl_3$, δ ppm) 7.37-7.29 (m, 6 H), 7.19 (AA'XX' pattern, *J* = 8.4 Hz, 2 H), 7.15 (AA'XX' pattern, *J* = 8.4 Hz, 2 H), 6.81 (AA'XX' pattern, *J* =

8.4 Hz, 4 H), 5.69 (br s, 1 H), 5.10 (s, 2 H), 3.86 (s, 3 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.63 (s, 2 H), 3.54 (s, 2 H), 3.23 (d, *J* = 13.6 Hz, 1 H), 3.22 (d, *J* = 13.6 Hz, 1 H), 3.16 (d, *J* = 13.6 Hz, 1 H), 2.95 (d, *J* = 13.6 Hz, 1 H), 2.55 (s, 3 H), 1.73 (s, 3 H), 1.55 (s, 3 H); ^{13}C NMR ($CDCl_3$, δ ppm) 172.3, 163.2, 162.5, 158.7, 158.6, 156.4, 154.9, 136.2, 129.9, 129.85, 129.85, 129.7, 128.4, 128.1, 128.0, 127.3, 113.9, 113.85, 66.7, 60.1, 55.9, 55.15, 55.1, 51.8, 40.0, 38.5, 37.1, 36.7, 23.7, 23.2, 12.0; HRMS *m/z* (M+H) calcd 722.2570, found 722.2555. Anal. Calcd for $C_{37}H_{44}N_3O_8S_2$: C, 61.48; H, 6.14; N, 5.81; S, 8.87. Found: C, 61.54; H, 6.23; N, 6.00; S, 8.71.

(*R*,*R*)-2-[2-Benzylsulfanyl-1-[(2-isopropyl-4-methyl-4,5-dihydrothiazole-4-carbonyl)amino]-1-methylethyl]-5-methyloxazole-4-carboxylic acid methyl ester (28c). Compound (**24c**) (35.8 mg, 0.060 mmol) was dissolved in acetonitrile (0.75 mL), P_4S_{10} was added (53.3 mg, 0.120 mmol), and the mixture heated at 55 °C, with stirring, for 24 h. The reaction mixture was poured into 10% aq. Na_2CO_3, stirred, and extracted twice with CH_2Cl_2. The combined CH_2Cl_2 layers were dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (2:1 hexane/EtOAc). The product was obtained as a clear colorless oil (20.0 mg, 68%): TLC R_f 0.29 (2:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$, δ ppm) 7.78 (br s, 1 H), 7.35-7.22 (m, 5 H), 3.62 (m, 3 H), 3.36 (d, *J* = 13.6 Hz, 1 H), 3.23 (d, *J* = 13.6 Hz, 1 H), 3.17 (d, *J* = 11.6 Hz, 1 H), 2.83 (heptet, *J* = 6.8 Hz, 1 H), 2.58 (s, 3 H), 1.79 (s, 3 H), 1.52 (s, 3 H), 1.29 (d, *J* = 6.8 Hz, 6 H); ^{13}C NMR ($CDCl_3$, δ ppm) 174.5, 163.2, 162.5, 156.4, 137.8, 128.7, 128.4, 127.3, 127.1, 126.9, 84.4, 56.0, 51.8, 41.2, 39.8, 37.3, 34.0, 24.5, 24.1, 21.0, 20.9, 12.0; FAB LRMS *m/z* (M+H) 490.2.

(*R*,*R*)-2-[1-[(2-Isopropyl-4-methyl-4,5-dihydrothiazole-4-carbonyl)amino]-2-(4-methoxybenzylsulfanyl)-1-methyl-ethyl]-5-methyloxazole-4-carboxylic acid methyl ester (28j). Following the procedure described for synthesis of **28c**, the product was obtained as a clear colorless oil (30%): ^{1}H NMR ($CDCl_3$, δ ppm) 7.82 (br s, 1 H), 7.18 (AA'XX' pattern, *J* = 8.4 Hz, 2 H), 6.83 (AA'XX' pattern, *J* = 8.4 Hz, 2 H), 3.88 (s, 3 H), 3.80 (s, 3 H), 3.67 (br d, *J* = 13.6 Hz, 1 H), 3.61 (d, *J* = 13.2 Hz, 1 H), 3.57 (d, *J* = 13.2 Hz, 1 H), 3.32 (d, *J* = 13.2 Hz, 1 H), 3.23 (d, *J* = 13.6 Hz, 1 H), 3.15 (d, *J* = 13.2 Hz, 1 H), 2.87 (heptet, *J* = 6.8 Hz, 1 H), 2.58 (s, 3 H), 1.78 (s, 3 H), 1.53 (s, 3 H), 1.31 (d, *J* = 6.8 Hz, 3 H), 1.25 (d, *J* = 6.8 Hz, 3 H); FAB LRMS *m/z* (M+H) 520.

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